PARP Inhibitors for Ovarian Cancer: Current Indications, Future Combinations, and Novel Assets in Development to Target DNA Damage Repair

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overview

PARP inhibitors (PARPIs) have revolutionized the treatment of epithelial ovarian cancer, first for BRCA-associated cancer, and, recently, for all epithelial cancers of serous or high-grade endometrioid subtypes in the front line. Although there is hope that PARPIs will help prevent recurrences when used following frontline maintenance, cancer will still recur in most women, and the need for active combination strategies as well as continued development of novel assets, either as monotherapy or in combination, will be urgently needed. This review article discusses the current indications for PARPIs in both frontline and recurrent settings, current research in combination approaches, and finally, ongoing research on novel methods to target DNA damage response in an effort to exploit the common susceptibility to DNA damage repair in epithelial ovarian cancer and improve outcomes for patients.

PARP INHIBITORS: FOR WHOM, WHEN, AND HOW?

The treatment paradigm for epithelial ovarian cancer (EOC), and, in particular, high-grade serous ovarian cancer (HGSOC), has been changing rapidly over the past 5 years. The typical course of EOC has been well established for decades. Women present, usually with advanced stage disease; they undergo a combination of paclitaxel and carboplatin chemotherapy and surgical cytoreduction as part of frontline management; and they commonly achieve a state of clinical remission, but unfortunately 80% will have recurrence of cancer within 3 years of diagnosis. Once recurred, the disease is no longer curable but fortunately treatable for many years. Treatment decisions are based on many factors inclusive of the time interval from last platinum therapy, histology, molecular profile, residual toxicities, and resectability. Despite many options for treatment in the recurrent setting, the disease becomes eventually resistant to all interventions, and women succumb to their disease.[1,2]

The most contemporary clinical trial to evaluate different delivery schedules for paclitaxel and carboplatin (and likely the last to do so) was ICON8, which compared standard every 21-day dosing with weekly paclitaxel and every 21-day carboplatin with weekly dosing of both paclitaxel and carboplatin. No maintenance was used. There was no difference in progression-free survival (PFS), making every 21-day paclitaxel and carboplatin the preferred option. In addition, this study provided the benchmark for median PFS in a study of advanced EOC without selection by histology or molecular subtype of 17.9 months.[3] The first big paradigm shift in frontline EOC (again, unselected by histology or molecular subtype) was the addition of bevacizumab with and to follow frontline therapy, which resulted in an improvement in PFS by approximately 4 months but no improvement in overall survival (OS).[4,5]

Perhaps the most important discovery for EOC and progress in outcomes is that EOC is not one disease but at least five: HGSOC, endometriod, clear cell, mucinous, and low-grade serous.[6] Each of these have unique molecular signatures and targets. Pulling out specific subtypes has led to the transformative and rapid introduction of PARP inhibitors (PARPIs) into the treatment paradigm. In particular, the recognition of homologous recombination deficiency (HRD) as an important and potential predictive biomarker for EOC and HGSOC has led to new indications for PARPIs across the treatment spectrum. As a reminder, homologous recombination (HR) is the high-fidelity process by which double strand DNA damage is repaired. It uses sister chromatids as the template, occurs in the G2/M phase of the cell cycle, and is dependent on the presence of proteins encoded by *BRCA1*, *BRCA2*, and others in the Fanconi anemia pathway for its function. The PARP 1 protein is also important because it recruits MRE11 and NBS1 to the

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PRACTICAL APPLICATIONS

- Women with BRCA-associated ovarian cancer should be offered maintenance therapy with olaparib or niraparib for 2–3 years.
- Women with epithelial ovarian cancer (high-grade serous, high-grade endometrioid) may be offered olaparib or niraparib following complete or partial response to platinum-based ovarian cancer.
- Women who are treated with bevacizumab concurrent with platinum-based chemotherapy and who have high grade serous or endometrioid cancer may have olaparib added as maintenance for up to 2 years following complete or partial response to therapy.
- Women with recurrent disease who respond to repeated use of platinum-based chemotherapy and have not previously received a PARPI, may be offered PARPI maintenance with olaparib or niraparib to continue until toxicity or progression.
- Women with recurrent disease that is associated with BRCA may use olaparib ($\geq$ 3 previous lines), rucaparib ($\geq$ 2 previous lines), or niraparib (homologous recombination deficient, platinum sensitive, $>$ 3 previous lines).

site of DNA damage as well as blocks entry into non-homologous end joining (NHEJ), which is the low-fidelity manner by which double strand DNA may be repaired. In cells with loss of proteins key to HR, inhibition of PARP leads to complete loss of HR and entry into NHEJ, which repairs DNA in an error-prone manner and leads to accumulation of DNA damage and cell death.[7-9]

HR proficiency appears to be lost in 50% of HGSOC, with approximately 30% loss due to germline (14%), somatic (6%), or epigenetic (10%) loss of *BRCA1* or *2* function (epigenetic changes are reported for *BRCA1* only). An additional 11% of HGSOC tumors harbor HRD due to other mutations in CDK1/2, Fanconi anemia genes, core RAD gene mutations, HR DNA damage gene mutations, or promoter methylation of RAD51C. Approximately 30% of HGSOC may have other alterations that do not cause HRD but still render tumors sensitive to PARPIs (e.g., nucleotide excision repair [NER] mutations and MMR mutations); these are under study. Fifteen percent of HGSOCs have cyclin E1 (CCNE1) amplification and are not sensitive to PARPIs.[10] Because of the prevalence of HRD, exploration of PARPIs in HGSOC (and high-grade endometrioid) was warranted, and, as of this report, completed as a part of frontline therapy, platinum-sensitive recurrent therapy (both single-agent treatment and maintenance), and among more heavily pretreated patients with recurrent disease. This article summarizes the data published to date in these three treatment settings, with the caveat that data presented at the 2020 ASCO Annual Meeting will affect how PARPIs use continues to evolve.

Frontline Maintenance

The potential for PARPI use to be transformative in frontline EOC was first demonstrated in the SOLO-1 study. Women with *BRCA*-associated, advanced HGSOC, or endometrioid cancer who achieved a complete response (CR) or partial response (PR) to frontline, platinum-based therapy were randomly assigned 2:1 to receive olaparib versus placebo until progression or 2 years. Use of maintenance olaparib in this setting led to a hazard ratio of 0.30 (95% CI, 0.23–0.41) and median PFS (not including time of chemotherapy) of approximately 49 months versus 13.8 months. OS was immature.[11] Exploratory analysis in women who entered the study with primary versus interval surgery demonstrated similar hazard ratio benefits (0.31 and 0.37, respectively). Similarly, women who entered the study with no residual versus residual disease benefitted from olaparib maintenance with hazard ratios of 0.33 and 0.44, respectively. Among the "best prognostic" group of women who entered a study with primary cytoreduction to no gross residual, the hazard ratio was 0.32 with 71% PFS versus 35% PFS at 3 years.[12] Based on this data, olaparib gained U.S. Food and Drug Administration approval for use as maintenance following frontline chemotherapy in BRCA-associated ovarian cancer in January 2019.

As stated previously, there are alterations beyond BRCA that indicate HRD and PARPIs may work for these patients as well. Because of the lack of a proven test to definitely identify those patients with HRD compared with homologous recombination proficient (HRp), three studies were completed that allowed all comers to enroll with appropriate stratification. These were the PRIMA, PAOLA1, and Velia studies.

PRIMA/ENGOT-OV26/GOG3012 enrolled women with HGSOC or endometrioid, advanced-stage, high-risk cancer (stage IV, neoadjuvant chemotherapy or residual disease following primary cytoreduction) who were in CR or PR following frontline paclitaxel and carboplatin therapy. This study randomly assigned participants 2:1 to receive niraparib or placebo until progression or 3 years. Stratification factors included HR status using an assay that tested loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions. Women were classified as having HRD if the score was 42 or higher. The primary endpoint for PRIMA was PFS in the intention-to-treat population (ITT) and the HRD population as determined by blinded radiographic review. This endpoint had a hazard ratio of 0.62 (95% CI, 0.5–0.76; $p < .001$) and median PFS of 13.8 months versus

8.2 months. In the HRD population, the hazard ratio was 0.43 (95% CI, 0.31–0.59; p = .001) and median PFS was 21.9 months versus 10.4 months. This population included those patients with BRCA-associated cancers. In exploratory nonhypothesis-tested analysis, the hazard ratio among only BRCA-associated cancers was 0.40 (95% CI, 0.27–0.62), among HRD/wild-type (BRCAwt) was 0.50 (95% CI, 0.31–0.83), and among HRp was 0.68 (95% CI, 0.49–0.94).[13]

PAOLA-1/ENGOT-OV25 enrolled women with HGSOC or endometrioid, advanced-stage cancers who were in CR or PR following frontline, platinum-based chemotherapy, including bevacizumab. They were then randomly selected 2:1 to continue bevacizumab with olaparib, added for 2 years or until progression versus placebo and bevacizumab. The primary endpoint was investigator-assessed PFS in the ITT population, and stratification was by BRCA-associated cancers. The hazard ratio was 0.59 (95% CI, 0.49–0.72; p < .0001) in favor of the addition of olaparib, with a median PFS of 22.1 months versus 16.6 months (this study had an active control compared with only placebo).[14] Exploratory nonhypothesis-tested endpoints included outcomes among only BRCA-associated cancers, with a hazard ratio of 0.31 (95% CI, 0.2–0.47), a BRCAwt hazard ratio of 0.71 (95% CI, 0.58–0.88), an HRD hazard ratio of 0.33 (95% CI, 0.25–0.45), an HRD/BRCAwt hazard ratio of 0.43 (95% CI, 0.28–0.66), and an HRp/ukn hazard ratio of 0.92 (95% CI, 0.72–1.17).[14]

Velia/GOG 3005 differed from the other studies in that it attempted to incorporate the PARPI veliparib with and to follow chemotherapy. Eligible patients had HGSOC and advanced-stage disease and were enrolled at the time of chemotherapy initiation. Randomization was 1:1:1 to carboplatin/paclitaxel/veliparib followed by veliparib maintenance (arm 1), carboplatin/paclitaxel/veliparib followed by placebo maintenance (arm 2), and carboplatin/paclitaxel/placebo followed by placebo maintenance (arm 3). The primary endpoint was PFS for arm 1 versus arm 3 in the ITT- and BRCA-associated cancers. Stratification factors included BRCA status. For the ITT group, the hazard ratio was 0.68 (95% CI, 0.56–0.83; p < .001) and median PFS was 23.5 months versus 17.3 months. Among the BRCA population, the hazard ratio was 0.44 (95% CI, 0.28–0.68; p < .001) and median PFS of 34.7 months versus 22 months. These PFS values were inclusive of time on chemotherapy and that all patients who started the trial contributed to the PFS, including those with stable disease or progressive disease during chemotherapy. Exploratory nonhypothesis-tested cohorts included patients with BRCAwt with a hazard ratio of 0.80 (95% CI, 0.64–0.997) and a median PFS of 18.2 months versus 15.1 months; an HRD/BRCAwt hazard ratio of 0.74 (95% CI, 0.52–1.06) and median PFS of 22.9 versus 19.8; an HRp hazard ratio of 0.81 (95% CI, 0.60–1.09) and median PFS of 15 months versus 11.5 months (Table 1).[15]

Ultimately, how these assets are used will depend on the indications allowed by regulatory agencies, which are all still pending at the time of writing, but anticipated in May 2020. Assuming that PAOLA-1 and PRIMA trials gain regulatory approval, the key questions will be: (1) do women with BRCA-associated cancers need bevacizumab and/or olaparib enough; and (2) although PRIMA was positive for ITT (for women with HRp tumors), is niraparib equivalent, better, or less effective than bevacizumab? Neither question has level 1 evidence to guide response; however, recent data presented at the Society for Gynecologic Oncology (SGO) 2020 meeting attempted to compare SOLO-1 and PAOLA-1 using a population-adjusted indirect treatment comparison to compare olaparib plus bevacizumab versus olaparib monotherapy, olaparib monotherapy versus bevacizumab monotherapy, and bevacizumab monotherapy versus placebo among women with BRCA-associated cancers. For the first comparison of olaparib plus bevacizumab versus olaparib, the hazard ratio was 0.71 (95% CI, 0.454–1.09), for olaparib monotherapy versus bevacizumab monotherapy, the hazard ratio was 0.48 (95% CI, 0.30–0.75), and for bevacizumab versus placebo, the hazard ratio was 0.65 (95% CI, 0.43–0.95). This exploratory analysis suggested a potential additive benefit of bevacizumab to olaparib among women with BRCA-associated cancers and reinforced the understanding that, although an active asset, bevacizumab was not equivalent to olaparib as monotherapy maintenance in this population.[16] As to the second question concerning efficacy among patients with HRp, both accurate identification of patients whose tumor truly is proficient in HR, and evaluating effective therapies are high, as of yet unmet, needs. In all studies, use of HRD assays failed to identify patients who would not benefit from PARPI maintenance. In another exploratory analysis presented at SGO 2020, Swisher et al evaluated the association of the Myriad myChoice Genomic Instability Score with PFS among patients with BRCAwt in the VELIA trial. Regardless of what Genomic Instability Score cutpoint was selected, there was PFS benefit in patients categorized as HRp and HRD and therefore did not have a predictive roll for PFS benefit in this trial.[17] Therefore, we can speculate that there is a benefit of PARPIs in patients currently classified as HRp, but we cannot speculate on the magnitude of benefit in this population for PARPIs versus bevavcizumab. That will have to await another trial.

Platinum-Sensitive Disease: Maintenance and Treatment

The first full approvals for PARPIs came from three phase III studies and one phase II study that evaluated PARPIs as maintenance following response to platinum-based therapy in the recurrent setting. Although all four studies had some

TABLE 1. Key Phase III Studies of PARP Inhibitors in Frontline Ovarian Cancer

Study	BRCA Status	Study Starts With	Study Arm	Control Arm	ITT	BRCAm	HRD	HRD/BRCAwt	HRp
SOLO1[11]	BRCA+	Maint	Olaparib	Placebo	NA	HR, 0.30* (0.23–0.41); mPFS: NR vs. 13.8	NA	NA	NA
PRIMA[13]	All comers	Maint	Niraparib	Placebo	HR, 0.62* (0.50–0.76); mPFS: 13.8 vs. 8.2	HR, 0.40 (0.27–0.62)	HR, 0.43* (0.31–0.59); mPFS: 21.9 vs. 10.4	HR, 0.50 (0.31–0.83)	HR, 0.68 (0.49–0.94)
PAOLA1[14]	All comers	Maint	Olaparib + Bev	Placebo + Bev	HR, 0.59* (0.49–0.72); mPFS: 22.1 vs. 16.6	HR, 0.31 (0.20–0.47); mPFS: 37 vs. 22	HR, 0.33 (0.25–0.45); mPFS: 37 vs. 17.7	HR, 0.43 (0.28–0.66); mPFS: 28.1 vs. 16.6	HR, 0.92 (0.72–1.17); mPFS: 16.9 vs. 16
VELIA[15]	All comers	With chemo	Veliparib	Placebo	HR, 0.68* (0.56–0.83); mPFS: 23.5 vs. 17.3	HR, 0.44* (0.28–0.68); mPFS: 34.7 vs. 22	NR	HR, 0.74 (0.52–1.06); mPFS: 22.9 vs. 19.8	HR, 0.81 (0.60–1.09); mPFS: 15 vs. 11.5

*Primary endpoints.

Abbreviations: Bev, bevacizumab; BRCAwt, wild-type BRCA; HR, hazard ratio; HRp, homologous recombination proficient; HRD, homologous recombination deficiency; ITT, intention to treat; Maint, maintenance; mPFS, median progression-free survival; NR, not reported.

differences in design, they were largely similar because they enrolled women with CR or PR to platinum-based therapy in the recurrent setting who were randomized to either PARPIs or placebo. The ARIEL3, NOVA, and Study 19 trials enrolled all comers, and SOLO 2 enrolled only those with *BRCA*-associated cancers. Table 2 summarizes the key findings of these trials. Interestingly, PARPI maintenance was effective in all treatment subgroups, *BRCA*-associated cancers, HRD, and HRp. This finding, compared with the seemingly poorer efficacy in HRp in the front line, could be explained by the fact that in the recurrent setting, we had a clinical biomarker of platinum sensitive to identify, one perhaps better than current assays, which benefits from PARPI maintenance.

Finally, there were single-arm phase II data and randomized phase III data that provide efficacy data for use of PARPI for treatment of ovarian cancer, instead of chemotherapy not following chemotherapy. Olaparib was the first PARPI approved in EOC for women with BRCA-associated cancers who received three or more lines of chemotherapy.[22] This was followed by rucaparib, which was approved in women with both germline and somatic *BRCA*-associated cancer who received two or more lines of chemotherapy.[23] Recently, SOLO-3 evaluated olaparib compared with investigator choice chemotherapy in a randomized phase III study among women with recurrent *BRCA*-associated EOC who were considered sensitive to platinum and received more than three lines of chemotherapy. Notably, there was no platinum among the investigator choice options; however, the study was declared positive based on an odds rate ratio of 72% versus 51% (odds ratio [OR], 2.53; 95% CI, 1.40–4.58; p = .002).[24] Niraparib was studied and approved in women with recurrent EOC whose tumors had evidence of HRD based on the QUADRA study (Table 3).[25]

Currently, PARPIs are indicated in frontline OC as maintenance for patients with BRCA-associated cancer who are in CR or PR following chemotherapy. PARPIs may be indicated beyond BRCA following potential results announced during the 2020 ASCO Annual Meeting. PARPIs are indicated as maintenance therapy following response to platinum-based chemotherapy without reference to BRCA status because of the power of the clinical biomarker: platinum sensitivity. Finally, for women with recurrent, PARPI-naïve disease, PARPIs are available as treatment instead of chemotherapy for women with BRCA-associated and HRD+ recurrent disease. New challenges include evaluation efficacy with repeat PARPIs use and combinations that improve outcomes among women who have HRp or who otherwise do not benefit from a monotherapy PARPI.

PARP INHIBITOR THERAPY: CURRENT CHALLENGES AND FUTURE OPPORTUNITIES

Women with HRD, in particular *BRCA1/2*-mutated HGSOC, greatly benefit from PARPI therapy.[26] However, because of the lack of a measurable surrogate to evaluate HRD in the clinic, PARPI approval has been granted as maintenance treatment in HGSOC post-response to platinum, regardless of HRD status. In addition, besides HRD, high replication

TABLE 2. Key Phase II and III Studies of PARP Inhibitors in Platinum-Sensitive Recurrent Disease

Study	Study 19[18]	SOLO-2[19] g*BRCA*m	NOVA[20] g*BRCA*m	NOVA[20] non*gBRCA*m	ARIEL-3[21] *BRCA*m	ARIEL-3[21] ITT
Agent	Olaparib	Olaparib	Niraparib	Niraparib	Rucaparib	Rucaparib
Difference in PFS (months)	8.4 vs. 4.8	19.1 vs. 5.5	21.0 vs. 5.5	9.3 vs. 3.9	16.6 vs. 5.4	10.8 vs. 5.4
PFS HR (investigator assessed)	**0.35** (95% CI, 0.25 –0.49; p < .001)	**0.30** (95% CI, 0.22–0.41; p < .0001)	**0.27** (95% CI, 0.18–0.40)	**0.53** (95% CI, 0.41–0.68)	**0.23** (95% CI, 0.16–0.34, p < .0001)	**0.36** (95% CI, 0.30–0.45; p < .0001)
PFS HR (BICR)	**0.39** (95% CI, 0.27– 0.55; p < .001)	**0.25** (95% CI, 0.18-0.35; p < .0001)	**0.27** (95% CI, 0.17–0.41; p < .0001)	**0.45** (95% CI, 0.34– 0.61; p < .0001)	**0.20** (95% CI, 0.13–0.32; p < .0001)	**0.35** (95% CI, 0.28–0.45; p < .0001)

Abbreviations: BICR, blinded radiographic review; HR, hazard ratio; PFS, progression-free survival.

stress induced by either loss of tumor suppressor gene or oncogene amplification can contribute toward PARPI sensitivity.[27] Although PARPIs have led to considerable benefit in women with HGSOC, patient selection remains a challenge. Not all patients benefit from this treatment, and response is not definitive, resulting in long-term use of the drug and development of resistance. Efforts are ongoing to identify potential ways to augment the overall benefit of PARPIs in women's cancer. This involves (1) deeper understanding of the landscape of PARPI response mechanisms and ways to overcome resistance; and (2) identifying new strategies to enhance the scope of PARPIs through combining PARPIs with other therapies (Fig. 1).

Understanding PARPI Resistance Mechanisms

As PARPIs move earlier into the treatment paradigm, identifying mechanisms of primary and acquired resistance is key to guide treatment and prevent recurrence. Following approval of various PARPIs, drug resistance has emerged in practice; yet, no standard treatment has been established for post-PARPI progression. Several PARPI resistance mechanisms have been described in the literature,[28,29] including: (1) increased drug efflux, such as overexpression of the multidrug resistance gene, *ABCB1,* which involves the promoter fusion of this gene[30]; (2) loss of PARP 1 function due to mutation or deletion[31,32]; (3) loss of PARG (poly [ADP-ribose] glycohydrolase) and restoration of PARylation[33]; (4) stabilization of stalled forks[34]; and (5) restoration of HR function.

Several of these mechanisms can lead tumors to switch from a HR-deficient to a HR-proficient state, and thereby, develop PARPI resistance. The most common mechanism is through the restoration of the expression or function of key proteins in the HR pathway by the acquisition of secondary mutations, also known as "reversion mutations." Reversion mutations in multiple HR pathway genes, including *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, and *PALB2* have been reported in both preclinical and clinical studies[35-40] and have enabled a functional restoration of the HR defect. Wild-type *BRCA1* levels or functionality may also be restored through demethylation of its hypermethylated promoter or intronic Alu-mediated gene rearrangements.[41,42] In addition, HR can be re-activated by suppressing the HR-counteracting pathway, NHEJ, with the loss of proteins involved in NHEJ (e.g., TP53BP1, RIF1, and REV7), which result in PARPI resistance.[43,44]

Another important mechanism of PARPI resistance is the stabilization of the stalled replication fork.[30] At the time of DNA damage, the cell cycle is halted, which allows cells to repair the damaged DNA with the aid of BRCA1/2, which acts by stabilization of the stalled replication forks. In BRCA1/2 deficient tumors, these stalled forks are subjected to MRE11- and MUS81-mediated degradation. PARPIs

TABLE 3. Single-Agent PARP Inhibitor in Epithelial Ovarian Cancer

Study	Study 1[22]	ARIEL2/Study 102 BRCAm[23]	ARIEL2/Study 102, BRCAwt[23]	QUADRA gBRCAm[25]	QUADRA HRD+[25]	SOLO3[24]	SOLO3[24]
Agent	Olaparib	Rucaparib	Rucaparib	Niraparib	Niraparib	Olaparib	IC
ORR	34% (95% CI, 26–42)	53.8% (95% CI, 44–64)	29% (LOH high) 10% (LOH low)	29%	27%	72%	51%
DOR	7.9 months (95% CI, 5.6–9.6)	9.2 months (95% CI, 6.6–11.6)	10.8 (5.7-NR) LOH-H 5.6 (4.6–8.5) LOH-L	8.3 (6.6–NR)	9.2 (5.9–15.2)	9.4 (5.6–25.7)	10.2 (5.5–15.3)
LOT	≥ 3	≥ 2	≥ 2	4th–5th line	4th–5th line	≥ 2	≥ 2

Abbreviations: DOR, duration of response; LOH, loss of heterozygosity; LOT, line of therapy; ORR, overall response rate.

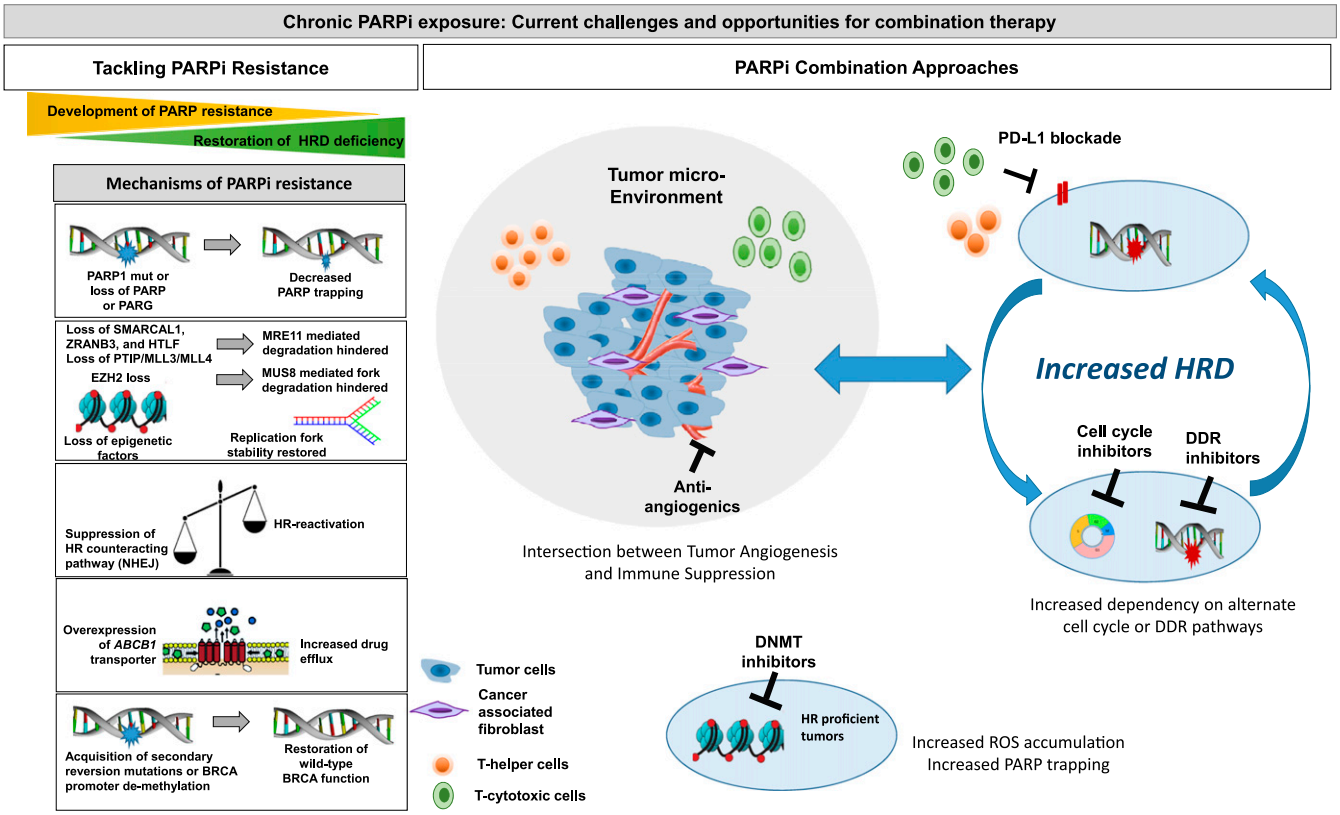

FIGURE 1. Challenges and Opportunities Using Combinatorial Approaches Following Long-Term PARP Exposure

(A) Varied genetic, epigenetic, and functional PARP inhibitor (PARPi) resistance mechanisms are described. (B) Current PARPi therapy can be enhanced using various combinatorial approaches targeting the tumor immune–microenvironment axis.

Abbreviations: DDR, DNA damage repair; DNMTi, DNA methyltransferase inhibitor; HR, homologous recombination; HRD, homologous recombination deficiency; NHEJ, nonhomologous end joining; ROS, reactive oxygen species.

further act upon this destabilized replication fork, which leads to their catastrophic degradation. There are three mechanisms described in the literature that are involved in fork degradation.[29] Loss of factors involved in these mechanisms may lead to fork protection or stabilization, and thereby, PARPI resistance. The first mechanism involves fork reversal by chromatin remodelers (e.g., SMARCAL1, ZRANB3, and HTLF), which, in turn, mediate MRE11-dependent fork degradation.[29] The second mechanism involves EZH2-mediated methylation of histone H3 at lysine 27 (H3K27), which then relays MUS8-mediated fork degradation.[29] Lastly, methylation of H3K4 by the histone methyltransferase complex of PTIP, MLL3, and MLL4 also leads to MRE11-mediated fork degradation.[29] Besides these mechanisms, the loss of the replication stress effector, SLFN11, may also contribute to PARPI resistance.[29]

Recently, new evidence hinted toward involvement of epigenetic factors in PARPI resistance. A preclinical study utilizing HGSOC cell lines and in vivo patient-derived xenograft models showed that PARPI-resistant HGSOC tumor cells exhibited increased levels of histone H3 lysine 9 (H3K9me2) and histone-lysine-*N*-methyl transferases 1 and 2 (EHMT1/2).[45] These cells were re-sensitized to PARPI through disruption of *EHMT1/2* and involved DNA damage and cell cycle dysregulation.[45]

Although several mechanisms of PARPI resistance were identified in the preclinical settings and their repertoire seemed to increase over time, evidence toward their existence in the clinical setting are still limited. In practice, platinum sensitivity is more commonly used as a valuable indicator of response to PARPIs.[46] Because platinum chemotherapy induces DNA lesions as well as aberrant cell cycle and DNA repair signaling,[47] some of the mechanisms of platinum-based response and/or resistance may overlap with PARPI resistance. For example, *CCNE1* amplification, a well-described marker of platinum resistance in HGSOC, has been observed with poor response to PARPIs.[48,49] The other commonly observed resistance mechanisms in the clinic are reversion mutations in HR genes (*BRCA1/2*, *RAD51C/D,* and so on).[35,36,38,50] Recently, a pilot prospective

study showed that multiple mechanisms of resistance could be observed in patients post-PARPI progression, which highlighted that PARPI resistance was multifactorial.[51] These included reversion mutations in *BRCA1/2* and other HR genes, *ABCB1* upregulation, *CCNE1* amplification, and *SLFN11* downregulation.[51] Because multiple mechanisms can lead to the restoration of DNA repair function and PARPI resistance, patient-by-patient analysis is needed to identify the specific mechanism(s) of resistance involved for each patient.[52] Detecting the mechanism involved at the time of recurrence is important for the decision-making process and identifying potential new vulnerabilities to target. This is an area of active investigation, and current research focuses on: (1) measuring the net functional impact of the acquired mechanism(s) of resistance on the HR defect in a patient's clinical journey; and (2) identifying the pathways or cellular mechanisms that have been considerably altered due to acquisition of the diverse mechanisms of resistance.

Identifying New PARPI Combination Strategies

The rationale of PARPI combination is to enhance PARPI activity by targeting alternative DNA damage repair (DDR) dependencies and reprogramming the microenvironment to overcome the challenge of resistance.[52] Several combinatorial approaches in both HR deficient and proficient OC tumors are under investigation both in preclinical and clinical studies.

Combining With Chemotherapeutic Agents

Studies targeting different chemotherapeutic agents such as platinum, topoisomerase inhibitors, or DNA alkylating agents have been tested in combination with PARPIs in early-phase trials in OC and other solid tumors.[53] The combination may act synergistically by enhancing PARP trapping or its catalytic activity.[53] Alternatively, PARPIs may act through exploiting the cytotoxic activity of these agents.[53] The major limitation of this combination is overlapping toxicities and dosing issues, and thus, PARPIs support the sequential use of these therapies in patients who respond well to chemotherapy.

Combining With Other DDR or Cell Cycle Pathways Inhibitors

Another attractive approach is to combine PARPIs with other DDR inhibitors based on the rationale that PARPI-resistant cells exhibit enhanced dependency on other DNA repair or cell cycle mechanisms, which can then be exploited toward an effective combination.[54-57] Preclinical and early-phase clinical trials have shown promising results upon combining DDR and cell cycle inhibitors with PARPIs, targeting proteins such as ATR, Chk1/2, and Wee1. In preclinical studies, PARPI-resistant, *BRCA*-mutated cancer cells showed increased reliance on the ataxia-telangiectasia and Rad3-related (ATR) signaling pathway, and ATR inhibition was able to overcome PARPI resistance.[55,57,58] Several early-phase clinical trials investigating ATR and PARP inhibitors combinations are ongoing (NCT03682289, NCT02576444, NCT02723864, NCT03462342). Downstream of ATR/ATM are checkpoint kinases: CHK1/2, followed by Wee1 tyrosine kinase proteins, and those that mediate the G2-M checkpoint. Inhibition of CHK1/2 using prexasertib along with olaparib has shown early benefit in *BRCA*-mutated tumors in a phase I study of HGSOC and other advanced solids tumors.[59] Similarly, combining Wee1 kinase inhibitor (AZD1775) along with PARPIs in OC is currently underway in two phase II studies (NCT02576444 and NCT03579316). Besides ATR, CHK1/2, and WEE1, other DDR inhibitors currently under development can be potentially combined with PARPIs (e.g., ATM, DNA-PK, and POLθ).[60] Bone marrow toxicity is a major concern when combining two DDR inhibitors; therefore, careful dosing and sequential administration of the drug is an important consideration while designing trials for these combinations.[27,60]

Combining With Anti-Angiogenics

PARPIs and anti-angiogenics have shown synergy in preclinical studies. For example, cediranib-mediated induction of hypoxia leads to altered gene expression of DNA repair genes and thus impaired HR.[61] The combination of cediranib and olaparib is under investigation with several large ongoing clinical trials for recurrent OC after benefit was observed in phase II clinical trials (NCT02446600, NCT02502266, NCT02889900).[53] The synergy of this strategy was further confirmed in the clinic with the combination of the PARPI niraparib and anti-VEGF-A antibody, bevacizumab, investigated in a phase II trial for platinum-sensitive recurrent OC (NCT02354131).[62] Recently, olaparib and bevacizumab were approved in the frontline maintenance setting following a positive result from the randomized phase III PAOLA-1 trial (ENGOT-OV25, NCT02477644).[14]

At the time of PARPI progression, the addition of the anti-angiogenic cediranib, showed activity in some patients (NCT02681237),[51] highlighting the benefit of targeting simultaneous angiogenesis and the HRD pathway. This suggested the importance of the tumor microenvironment for enhancing PARPI activity. Combination with anti-angiogenics can be an attractive strategy, particularly in the HR proficient tumor or the post-PARPI setting.[51]

Combining With Immunotherapy

Recently, immune checkpoint inhibitors showed phenomenal response in patients with increased tumor mutation burden and led to therapeutic changes in pratice.[63,64] DDR deficiency was associated with higher tumor mutation burden,[27] and *BRCA1/2* or HR-deficient OC increased the neo-antigen load compared with HR-proficient tumors.[65]

PARPI treatment led to overexpression of *PD-L1*, which resulted in cancer-associated immunosuppression. Therefore, combining PD-L1 blockade therapy along with PARPIs might circumvent the problem of PARPI-led immune suppression and augment the efficacy of PARPI therapy.[66,67] In addition, PARPI administration led to acute inflammation, reprogramming of the tumor immune microenvironment, and a systemic immune response.[12,68] Because of the pharmacodynamics changes induced by PARPI, targeting the immune environment at the time of PARPI treatment seems attractive and is being tested in several clinical trials in the recurrent OC and frontline maintenance settings.[53]

Because of the intertwined regulation of angiogenesis and immune modulation, reprogramming the tumor microenvironment by combining anti-angiogenic agents and immunotherapy could enhance antitumor responses. Recent studies investigated triplet combinations of PARPIs, anti-angiogenics, and immune checkpoint inhibitors. The early results showed that the combination seemed tolerable with manageable side effects.[53] Larger clinical trials are ongoing to assess benefit.

Combining With Epigenetic Modulators

Another emerging combination that is actively under investigation in early-phase clinical trials are PARPIs with epigenetic or chromatin modifiers. There is preclinical evidence that combined inhibition of DNA methyltransferase inhibitors guadecitabine and PARPI talazoparib lead to decreased tumor growth in mouse models and increased OS.[69] The DNA methyltransferase inhibitor and PARPI combination led to increased reactive oxygen species accumulation and enhanced sensitivity of breast and OC cells to PARPI in a cAMP/PKA-dependent manner and through enhanced PARP trapping,[69] regardless of *BRCA* status. Recent evidence also showed the synergistic effect of the EZH2 inhibitor with PARPI in HR-proficient OC.[70]

In conclusion, several different approaches are currently underway, aiming to expand the repertoire of PARPI benefit by inducing HR deficiency in tumors and limiting emergence of resistance. However, the magnitude of success is dependent on careful rationalization of the choice of the combination based on the molecular and clinical attributes of an individual patient during the course of treatment.

BEYOND PARP INHIBITORS: TARGETING DNA DAMAGE CHECKPOINTS IN OVARIAN CANCER

The DDR signaling network preserves genomic integrity via the coordinated regulation of cell cycle progression and DNA repair.[9,60] This is orchestrated by the DNA damage checkpoint kinases ATM and ATR, which recognize DNA damage and phosphorylate key effector proteins to induce cell cycle arrest and facilitate DNA repair.[71,72] Because of their role as master regulators of DDR, ATM and ATR have long been the focus of drug discovery efforts, and inhibitors of these kinases are currently undergoing clinical evaluation as anticancer agents.[60,73]

Targeting the ATM-CHK2 DNA Damage Checkpoint

The ATM–CHK2 pathway primarily responds to DNA double strand breaks (DSBs) by promoting G1 arrest (via phosphorylation and activation of CHK2 and TP53) and DNA repair via activation of HRR or NHEJ.[74] ATM promotes HRR by recruiting BRCA1 to DSBs but can also promote NHEJ by antagonizing BRCA1 and recruiting TP53 binding protein 1 (53BP1).[74,75] These antagonistic functions are cell cycle regulated, whereby NHEJ is the predominant DSB repair mechanism used in the G1 phase, and whereas HRR is predominant in the S phase.[75] Germline mutations of ATM result in the well-characterized human autosomal recessive disorder ataxia-telangiectasia, which is associated with hypersensitivity to ionizing radiation, failure of cells to arrest the cell cycle after induction of DSBs, and an increased cancer predisposition (20%–30% lifetime cancer risk).[76] Somatic ATM alterations (mutations or deletions) are observed in a variety of cancers (including approximately 3% of ovarian cancers, 6% of cervical cancers, and 5% of uterine carcinosarcomas) and can be exploited by existing therapeutic modalities (e.g., PARPIs, radiation therapy, DSB-inducing chemotherapy agents) or emerging targeted therapies (e.g., ATR/WEE1/CHK1 inhibitors) that exhibit synthetic lethality to ATM-deficient cells.[77,78] Preclinical studies have demonstrated that inhibition of ATM induces radio- and chemo-sensitivity via diverse mechanisms, including abrogation of HRR and NHEJ.[79,80] Furthermore, ATM inhibitors exhibit synergistic activity with PARPs and ATR inhibitors in a variety of tumor models.[81-83] Although development of ATM inhibitors was reported as early as 2004, their clinical development is still lacking compared with other DDR-targeting agents. Two oral ATM inhibitors (AZD0156 and the brain-penetrant AZD1390) are currently under investigation in phase I clinical trials (NCT02588105 and NCT03423628), either alone, or in combination with chemotherapy, PARPIs, or radiation therapy.[84,85] In the phase I study of AZD0156 with olaparib (AToM Study, NCT02588105) in patients with advanced malignancies, doses of AZD0156 at 60 mg orally twice daily (bid) 3 days on/4 days off with olaparib 200 mg orally bid continuously were well tolerated, and pharmacokinetic evaluation indicated that AZD0156 exposure was consistent with efficacy in vitro.[85] Two confirmed PRs (one in a patient with germline BRCA2 mutation and one in a patient with unknown tumor genetics) were reported, whereas one patient with a tumor with somatic BRCA2 deletion exhibited stable disease for 18 months. Hematologic toxicity, consistent with the mechanism of action of both agents, was observed in higher doses of AZD0156 and represents the treatment-limited toxicity of

AZD0156/olaparib. Although there are currently no clinical trials of ATM inhibitors specifically for patients with OC or other gynecologic malignancies, exploration of ATM inhibition in this setting is warranted.

Targeting the ATR-CHK1-WEE1 DNA Damage Checkpoint

Although ATM/CHK2 signaling is triggered in response to DSB formation, ATR is activated by single-stranded DNA (ssDNA) that forms during replication stress or as an intermediate during DNA repair via HRR and NER.[71] Replication stress is defined as the slowing or stalling of replication fork progression during DNA synthesis.[71,74,86] Slowing or stalling of the replication forks leads to formation of ssDNA, which activates ATR kinase signaling that initiates a highly sophisticated replication stress response that involves cell cycle arrest, stabilization of replication forks, suppression of dormant origin firing (which helps prevent unscheduled DNA synthesis), and activation of DNA repair.[74,87] Activation of ATR triggers the intra-S phase and G2 checkpoints via phosphorylation of CHK1,[88] which, in turn, inactivates (by phosphorylation) CDC25 phosphatases CDC25A and CDC25C to inhibit cell cycle progression through the coordinate suppression of CDK2 and CDK1 (CDK2 and CDK1 facilitate entry into the *S* and M phases of the cell cycle, respectively).[71,74,89,90] Similarly, WEE1 kinase also inhibits both CDK1 and CDK2 (both via inhibitory phosphorylation) to prevent mitotic entry and replication initiation in the S phase.[88,91] Importantly, CHK1 has been reported to phosphorylate and activate the kinase activity of WEE1, suggesting that WEE1 kinase is downstream of ATR-CHK1, although this may be context-specific.[92,93] Finally, ATR facilitates DNA repair via phosphorylation of several proteins involved in HRR and Fanconi anemia/interstrand crosslink repair, including BRCA2, RAD51, FANCA, FANCI, FANCD2, and FANCE.[74,87]

Sources of replication stress that may lead to activation of ATR and initiation of the replication stress response include loss of the G1/S checkpoint, premature entry into the S phase, oncogenic drive, and DNA repair deficiencies (Fig. 2).[10,71,89] Cancer cells with high replication stress depend on ATR and the replication stress response for their survival. This cancer-specific dependency can be exploited therapeutically by pharmacologic inhibition of ATR, CHK1, or WEE1. Accordingly, ATR/CHK1/WEE1 inhibitors exhibit strong antitumor activity in tumor models with high replication stress, including models with *MYC* overexpression, *CDKN2A* deletion, *TP53* inactivation, *CCNE1* amplification, and DNA repair deficiencies (e.g., *BRCA1/2*- and *ATM*-mutated models).[90,94-96] It is important to underscore that although it has been proposed that WEE1 inhibitors and ATR inhibitors behave similarly, emerging data in lymphoma models using the ATR inhibitor AZD6738 and WEE1 inhibitor AZD1775 indicate that their mechanisms of action may be different.[96] Specifically, although ATR inhibition is associated with subsequent (daughter) G1 arrest and cell death (i.e., cells with high replication stress treated with ATR inhibitors enter mitosis and form DNA lesions detected as 53BP1 nuclear bodies and arrest in G1 phase in the subsequent cell cycle), WEE1 inhibition is more potent, inducing cell cycle arrest in the same cell cycle, with cells undergoing arrest and death in the S phase before entering mitosis, presumably due to replication catastrophe.[96]

All of the aforementioned mechanisms of replication stress are highly prevalent in HGSOC (Fig. 2).[77,98,99] Specifically, large-scale genomic studies demonstrated that HGSOC exhibit: (1) near universal loss of the G1/S checkpoint (via deleterious TP53 mutations); (2) premature S-phase entry due to *CCNE1* amplification, *RB1* loss, or CDKN2A mRNA downregulation; (3) oncogenic driver activation via amplification of the *MYC* oncogene or *NF1* loss; and (4) DNA repair deficiencies, mainly due to HRR alterations and less commonly due to NER alterations.[77,98,99] Because of the prevalence of increased replication stress in this histology, inhibition of ATR/CHK1/WEE1 signaling might be an effective strategy against these tumors. Accordingly, in an open-label, single-center, phase II study in *BRCA*wt HGSOC,[99] the CHK1 inhibitor prexasertib, administered intravenously at 105 mg/m^2 as monotherapy every 14 days, exhibited an objective response rate of 33% (8 of 24 patients, all PRs; Table 4). Four of the eight PRs involved tumors that exhibited both CCNE1 mRNA upregulation and *CCNE1* amplification or copy gain. Prexasertib is currently being evaluated in a larger multicenter study in ovarian cancer (NCT03414047). In addition, the WEE1 inhibitor AZD1775 as monotherapy was recently shown to have promising activity in uterine high-grade serous cancer (objective response rate, 29%; Table 4), another tumor type that, like HGSOC, is enriched with genomic alterations that lead to increased replication stress. ATR inhibitor monotherapy has not been evaluated specifically in OC or other gynecologic malignancies but has produced objective responses in *ATM*-mutated and/or *ATM*-deficient tumors, which is consistent with the preclinical data that indicate a synthetic lethal interaction between ATM and ATR inhibition.[83,90]

ATR inhibitors have been shown to sensitize OC cells to multiple genotoxic chemotherapy agents used routinely in this disease, including platinum agents, topoisomerase-I inhibitors, gemcitabine, and PARPIs.[100-103] Sensitization to these genotoxic agents has also been reported with WEE1 inhibitors.[95,104-107] All these agents induce replication stress and dependency on ATR via different mechanisms that culminate in the slowing and/or stalling of the replication of fork and the inhibition of DNA replication. Synergism with platinum is particularly potent, which can be explained by the additional role of ATR in the activation of the Faconi anemia and/or interstrand crosslink DNA repair pathway that is responsible for repair of the DNA interstrand

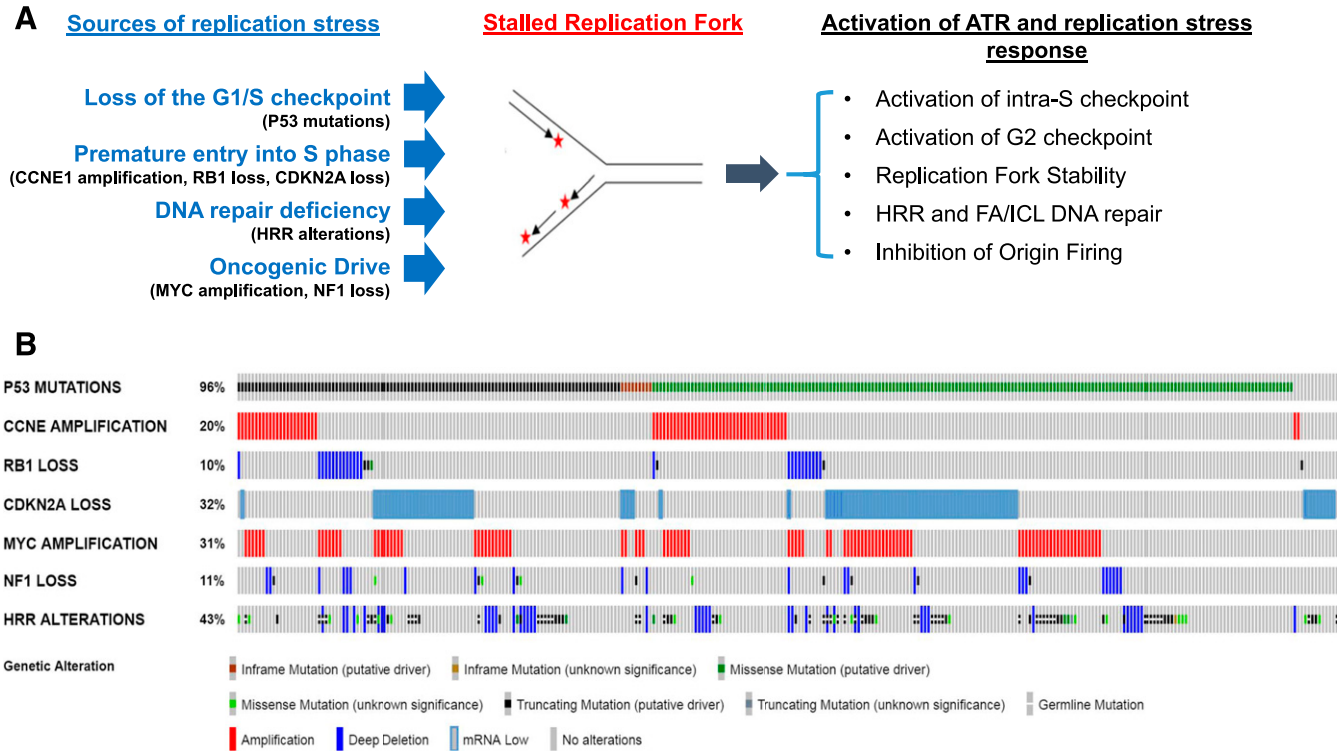

FIGURE 2. HGSOCs Exhibit High Replication Stress and Depend on ATR Kinase Activation and the Replication Stress Response

(A) Various mechanisms of replication stress lead to slowing/stalling of the replication fork, formation of single strand DNA that induces activation of ATR and the replication stress response. (B) Prevalence of various mechanisms of high replication stress in high-grade serous ovarian cancers (HGSOCs) of The Cancer Genome Atlas[77,97] highlighting that most HGSOCs exhibit at least two mechanisms of increased replication stress. Each column represents one HGSOC (n = 316).

Abbreviation: FA/ICL, Fanconi anemia/interstrand crosslink

crosslinks induced by platinum.[74,87] It is important to underscore that ATR inhibitors also sensitize *BRCA1/2*-mutated cells to platinum, topoisomerase-I inhibitors, and PARPIs, which is beyond the potent sensitization already caused by their defective HRR.[100] Preclinical studies have also demonstrated that ATR inhibitors may reverse resistance PARPIs in *BRCA1/2*-mutated models by addressing the two major mechanisms of resistance in this setting: (1) restoration of HRR; and (2) replication fork stabilization.[108,109] Other studies have also indicated synergism of ATR inhibitors with WEE1 inhibitors[96,110,111] and immune checkpoint inhibitors.[112] However, unlike ATR and WEE1 inhibitors that sensitize to a broad spectrum of genotoxic agents, available data suggest that CHK1 inhibitors might not uniformly sensitize to genotoxic drugs, which suggests different roles of ATR and CHK1 in the response to genotoxic chemotherapy.[95,99,113]

Table 4 summarizes the results of key phase II studies of ATR/WEE1/CHK1 inhibitors, alone or in combination in patients with OC or other gynecologic malignancies.[114-118] Three randomized phase II studies, two on the WEE1 inhibitor AZD1775 and one on the ATR inhibitor M6620, have suggested that addition of these agents to standard chemotherapy improves PFS in OC. Furthermore, one phase II study of AZD1775 and carboplatin in *TP53*-mutated, platinum-resistant and/or refractory OC showed a promising objective response rate of 43%. These results, combined with the prexasertib and AZD1775 monotherapy data in high-grade serous ovarian and uterine cancers as previously discussed, support further development of these agents in these tumors with high replication stress. Although preclinical data suggest that WEE1 inhibition as monotherapy may be more potent than ATR inhibition as monotherapy (as previously discussed), combinations of chemotherapy with ATR inhibitors appear to better tolerated than combinations with WEE1 inhibitors. Taken together, ATR inhibitor development may be more likely to succeed using combinatorial approaches, whereas WEE1 inhibition may be more likely to succeed as monotherapy. A major challenge for further development of these agents is the absence of predictive biomarkers of response. Although preclinical data indicate that *CCNE1* amplification, *MYC* amplification, *CDKN2A* loss,

TABLE 4. Key Phase II Studies of ATR/CHK1/WEE1 Inhibitors in Ovarian Cancer and Other Gynecologic Malignancies

Study Identifier	Agents	Target	Design	Patients/Accrual	Primary Endpoint	Results	Comments
NCT02151292	Gemcitabine/ AZD1775 (Adavosertib) vs. Gemcitabine/ placebo	WEE1	Multicenter, randomized, phase II, double-blind (2:1 randomization)	Platinum-resistant/refractory HGSOC, unlimited previous lines N=124	PFS	Median PFS: Gem/AZD1775: 4.6 months; Gem/Placebo: 3.0 months; HR, 0.56	In Gem/AZD1775: Thrombocytopenia G $\geq$ 3: 31%; Neutropenia G $\geq$ 3: 62%
NCT01164995	Carboplatin/ paclitaxel/ AZD1775 vs. Carboplatin/ paclitaxel/ placebo	WEE1	Multicenter, randomized, phase II, double-blind (1:1 randomization)	*TP53*-mutated ovarian cancer N = 121	PFS (volumetric RECIST 1.1.)	Median PFS: Carboplatin/paclitaxel/ AZD1775: 34.14 weeks; Carboplatin/paclitaxel/ placebo: 31.86 weeks; HR, 0.63	Carboplatin/paclitaxel/ AZD1775 G $\geq$ 3 AEs: 78%; Carbo/paclitaxel/placebo G $\geq$ 3 AEs: 65%
NCT02595892	Gemcitabine/ M6620 (Berzosertib) vs. Gemcitabine	ATR	Multicenter, randomized, phase II, open label (1:1 randomization)	Platinum-resistant HGSOC, unlimited previous lines but no more than 1 previous regimen in platinum-resistant setting N = 70	PFS	Median PFS: Gemcitabine/M6620: 22.9 wks; Gemcitabine: 14.7 wks; HR, 0.61	In Gem/M6620: Thrombocytopenia G $\geq$ 3: 24% In Gem alone: Thrombocytopenia G $\geq$ 3: 6%
NCT01164995	Carboplatin/ AZD1775	WEE1	Phase II, single arm	*TP53*-mutated ovarian cancer, refractory or resistant (< 3 months) to first-line platinum N = 21 (evaluable)	ORR	ORR: 43%, 9 patients (1 CR + 8 PR)	Thrombocytopenia G $\geq$ 3: 48%; Neutropenia G $\geq$ 3: 37%
NCT02203513	Prexasertib	CHK1	Phase II, single arm, single center	HGS or HG endometrioid ovarian cancer, germline BRCAwt N = 24 (evaluable)	ORR	ORR: 33%, 8 patients, all PRs, 4 of 8 PRs in tumors with CCNE1 overexpression	Thrombocytopenia G $\geq$ 3: 25%; Neutropenia G $\geq$ 3: 93%; Febrile neutropenia G $\geq$ 3: 7%
NCT03668340	AZD1775	WEE1	Phase II, single arm	Recurrent high-grade serous uterine cancer N = 34 (evaluable)	ORR and PFS	ORR: 29% PFS: 59%	Neutropenia G $\geq$ 3: 32%

Abbreviations: AE, adverse event; BRCAwt, wild-type BRCA; CR, complete response; HG, high grade; HGSOC, high-grade serous ovarian cancer; HGS, high-grade serous; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival, PR, partial response.

TP53 mutations, *ATM* deficiency, and HRR deficiency may predict response to ATR/CHK1/WEE1 inhibitors, clinical studies have not yet confirmed these (except for *ATM* deficiency being a predictor for response to ATR inhibition). Correlative work from these and future studies will hopefully identify biomarkers that can guide selection of patients that would be prime candidates for these therapies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Ledermann JA, Raja FA, Fotopoulou C, et al; ESMO Guidelines Working Group. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi24-vi32.
2. Wilson MK, Pujade-Lauraine E, Aoki D, et al; Participants of the Fifth Ovarian Cancer Consensus Conference. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: recurrent disease. Ann Oncol. 2017;28:727-732.
3. Clamp AR, James EC, McNeish IA, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. Lancet. 2019;394:2084-2095.
4. Burger RA, Brady MF, Bookman MA, et al; Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365:2473-2483.
5. Perren TJ, Swart AM, Pfisterer J, et al; ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011;365:2484-2496.
6. Vaughan S, Coward JI, Bast RC Jr., et al. Rethinking ovarian cancer: recommendations for improving outcomes. Nat Rev Cancer. 2011;11:719-725.
7. Walsh CS. Two decades beyond BRCA1/2: homologous recombination, hereditary cancer risk and a target for ovarian cancer therapy. Gynecol Oncol. 2015;137:343-350.
8. Konecny GE, Kristeleit RS. PARP inhibitors for BRCA1/2-mutated and sporadic ovarian cancer: current practice and future directions. Br J Cancer. 2016;115:1157-1173.
9. O'Connor MJ. Targeting the DNA damage response in cancer. Mol Cell. 2015;60:547-560.
10. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, et al. Homologous recombination deficiency: exploiting the fundamental vulnerability of ovarian cancer. Cancer Discov. 2015;5:1137-1154.
11. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379:2495-2505.
12. Mathews CMK, Colombo N, Scambia G, et al. Maintenance olaparib after platinum-based chemotherapy in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Efficacy by surgical and tumor status in the Phase III SOLO1 trial. J Clin Oncol. 2019;37 (suppl; abstr 5541).
13. González-Martín A, Pothuri B, Vergote I, et al; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019;381:2391-2402.
14. Ray-Coquard I, Pautier P, Pignata S, et al; PAOLA-1 Investigators. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med. 2019;381:2416-2428.
15. Coleman RL, Fleming GF, Brady MF, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019;381:2403-2415.
16. Vergote IMK, Hettle R, Rohodes K, et al. Population adjusted indirect comparison of the SOLO-1 and PAOLA-1/ENNGOT-ov25 studies of olaparib with or without bevacizumab, bevacizumab alone and placebo in the maintenance treatment of women with newly diagnosed stage III/IV ovarian cancer with BRCA mutation. Gynecol Oncol. 2020, In press.
17. Swisher EKS, Birrer MJ, Levine DA, et al. Exploring the relationship between homologous recombination score and progression free survival in BRCA wildtype ovarian carcinoma: analysis of velparib plus carboplatin/paclitaxel in the phase 3 VELIA/GOG 3005 study. Gynecol Oncol. 2020, In press.
18. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 2014;15:852-861.

19. Pujade-Lauraine E, Ledermann JA, Selle F, et al; SOLO2/ENGOT-Ov21 Investigators. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18:1274-1284.
20. Mirza MR, Monk BJ, Herrstedt J, et al; ENGOT-OV16/NOVA Investigators. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375:2154-2164.
21. Coleman RL, Oza AM, Lorusso D, et al; ARIEL3 Investigators. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390:1949-1961.
22. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33:244-250.
23. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol. 2017;18:75-87.
24. Penson RT, Valencia RV, Cibula D, et al. Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial. J Clin Oncol. Epub 2020 February 19.
25. Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2019;20:636-648.
26. Lord CJ, Ashworth A. PARP inhibitors: the first synthetic lethal targeted therapy. Science. 2017;355:1152-1158.
27. Pilié PG, Gay CM, Byers LA, et al. PARP inhibitors: extending benefit beyond BRCA-mutant cancers. Clin Cancer Res. 2019;25:3759-3771.
28. Wakefield MJ, Nesic K, Kondrashova O, et al. Diverse mechanisms of PARP inhibitor resistance in ovarian cancer. Biochim Biophys Acta Rev Cancer. 2019; 1872:188307.
29. Noordermeer SM, van Attikum H. PARP inhibitor resistance: a tug-of-war in BRCA-mutated cells. Trends Cell Biol. 2019;29:820-834.
30. Christie EL, Pattnaik S, Beach J, et al. Multiple ABCB1 transcriptional fusions in drug resistant high-grade serous ovarian and breast cancer. Nat Commun. 2019;10:1295.
31. Pettitt SJ, Krastev DB, Brandsma I, et al. Genome-wide and high-density CRISPR-Cas9 screens identify point mutations in PARP1 causing PARP inhibitor resistance. Nat Commun. 2018;9:1849.
32. Ding X, Ray Chaudhuri A, Callen E, et al. Synthetic viability by BRCA2 and PARP1/ARTD1 deficiencies. Nat Commun. 2016;7:12425.
33. Gogola E, Duarte AA, de Ruiter JR, et al. Selective loss of PARG restores PARylation and counteracts PARP inhibitor-mediated synthetic lethality. Cancer Cell. 2018;33:1078-1093.e12.
34. Liao H, Ji F, Helleday T, et al. Mechanisms for stalled replication fork stabilization: new targets for synthetic lethality strategies in cancer treatments. EMBO Rep. 2018;19:e46263.
35. Lin KK, Harrell MI, Oza AM, et al. BRCA reversion mutations in circulating tumor DNA predict primary and acquired resistance to the PARP inhibitor rucaparib in high-grade ovarian carcinoma. Cancer Discov. 2019;9:210-219.
36. Christie EL, Fereday S, Doig K, et al. Reversion of BRCA1/2 germline mutations detected in circulating tumor DNA from patients with high-grade serous ovarian cancer. J Clin Oncol. 2017;35:1274-1280.
37. Edwards SL, Brough R, Lord CJ, et al. Resistance to therapy caused by intragenic deletion in BRCA2. Nature. 2008;451:1111-1115.
38. Kondrashova O, Nguyen M, Shield-Artin K, et al; AOCS Study Group. Secondary somatic mutations restoring RAD51C and RAD51D associated with acquired resistance to the PARP inhibitor rucaparib in high-grade ovarian carcinoma. Cancer Discov. 2017;7:984-998.
39. Barber LJ, Sandhu S, Chen L, et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. J Pathol. 2013;229:422-429.
40. Goodall J, Mateo J, Yuan W, et al; TOPARP-A Investigators. Circulating cell-free DNA to guide prostate cancer treatment with PARP inhibition. Cancer Discov. 2017;7:1006-1017.
41. Wang Y, Bernhardy AJ, Nacson J, et al. BRCA1 intronic Alu elements drive gene rearrangements and PARP inhibitor resistance. Nat Commun. 2019;10:5661.
42. ter Brugge P, Kristel P, van der Burg E, et al. Mechanisms of therapy resistance in patient-derived xenograft models of BRCA1-deficient breast cancer. J Natl Cancer Inst. 2016;108:djw148.
43. Escribano-Díaz C, Orthwein A, Fradet-Turcotte A, et al. A cell cycle-dependent regulatory circuit composed of 53BP1-RIF1 and BRCA1-CtIP controls DNA repair pathway choice. Mol Cell. 2013;49:872-883.
44. Xu G, Chapman JR, Brandsma I, et al. REV7 counteracts DNA double-strand break resection and affects PARP inhibition. Nature. 2015;521:541-544.
45. Watson ZL, Yamamoto TM, McMellen A, et al. Histone methyltransferases EHMT1 and EHMT2 (GLP/G9A) maintain PARP inhibitor resistance in high-grade serous ovarian carcinoma. Clin Epigenetics. 2019;11:165.
46. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol. 2010;28:2512-2519.
47. Kelland L. The resurgence of platinum-based cancer chemotherapy. Nat Rev Cancer. 2007;7:573-584.
48. Nakayama N, Nakayama K, Shamima Y. Gene amplification *CCNE1* is related to poor survival and potential therapeutic target in ovarian cancer. Cancer. 2010; 116:2621-2634.

49. Wiedemeyer WR, Beach JA, Karlan BY. Reversing platinum resistance in high-grade serous ovarian carcinoma: targeting BRCA and the homologous recombination system. Front Oncol. 2014;4:34.

50. Quigley D, Alumkal JJ, Wyatt AW, et al. Analysis of circulating cell-free DNA identifies multiclonal heterogeneity of BRCA2 reversion mutations associated with resistance to PARP inhibitors. Cancer Discov. 2017;7:999-1005.

51. Lheureux S, Oaknin A, Garg S. Evolve: A Post PARP Inhibitor Clinical Translational Phase II Trial of Cediranib-Olaparib in Ovarian Cancer—A Princess Margaret Consortium – GCIG Phase II Trial. J Clin Oncol. 2019;37:15s (suppl; abstr 5521).

52. Lheureux S, Mirza M, Coleman R. The DNA repair pathway as a target for novel drugs in gynecologic cancers. J Clin Oncol. 2019;37:2449-2459.

53. Veneris JT, Matulonis UA, Liu JF, et al. Choosing wisely: selecting PARP inhibitor combinations to promote anti-tumor immune responses beyond BRCA mutations. Gynecol Oncol. 2019;156:488-497.

54. Murai J, Feng Y, Yu GK, et al. Resistance to PARP inhibitors by SLFN11 inactivation can be overcome by ATR inhibition. Oncotarget. 2016;7:76534-76550.

55. Kim H, George E, Ragland R, et al. Targeting the ATR/CHK1 axis with PARP inhibition results in tumor regression in BRCA-mutant ovarian cancer models. Clin Cancer Res. 2017;23:3097-3108.

56. Lallo A, Frese KK, Morrow CJ, et al. The combination of the PARP inhibitor olaparib and the Wee1 inhibitor AZD1775 as a new therapeutic option for small cell lung cancer. Clin Cancer Res. 2018;24:5153-5164.

57. Haynes B, Murai J, Lee J-M. Restored replication fork stabilization, a mechanism of PARP inhibitor resistance, can be overcome by cell cycle checkpoint inhibition. Cancer Treat Rev. 2018;71:1-7.

58. Yazinski SA, Comaills V, Buisson R, et al. ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells. Genes Dev. 2017;31:318-332.

59. Do KT, Hill SJ, Kochupurakkal B, et al. Phase I combination study of the CHK1 inhibitor prexasertib (LY2606368) and olaparib in patients with high-grade serous ovarian cancer and other advanced solid tumors. Cancer Res. 2019;79 (13 Suppl; abstr CT232).

60. Pilié PG, Tang C, Mills GB, et al. State-of-the-art strategies for targeting the DNA damage response in cancer. Nat Rev Clin Oncol. 2019;16:81-104.

61. Kaplan AR, Gueble SE, Liu Y, et al. Cediranib suppresses homology-directed DNA repair through down-regulation of BRCA1/2 and RAD51. Sci Transl Med. 2019;11:eaav4508.

62. Mirza MR, Åvall Lundqvist E, Birrer MJ, et al; AVANOVA Investigators. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol. 2019;20:1409-1419.

63. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med. 2018;379:341-351.

64. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med. 2018;378:1976-1986.

65. Strickland KC, Howitt BE, Shukla SA, et al. Association and prognostic significance of BRCA1/2-mutation status with neoantigen load, number of tumor-infiltrating lymphocytes and expression of PD-1/PD-L1 in high grade serous ovarian cancer. Oncotarget. 2016;7:13587-13598.

66. Sen T, Rodriguez BL, Chen L, et al. Targeting DNA damage response promotes antitumor immunity through STING-mediated T-cell activation in small cell lung cancer. Cancer Discov. 2019;9:646-661.

67. Jiao S, Xia W, Yamaguchi H, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res. 2017;23:3711-3720.

68. Chabanon RM, Muirhead G, Krastev DB, et al. PARP inhibition enhances tumor cell-intrinsic immunity in ERCC1-deficient non-small cell lung cancer. J Clin Invest. 2019;129:1211-1228.

69. Pulliam N, Fang F, Ozes AR, et al. An effective epigenetic-PARP inhibitor combination therapy for breast and ovarian cancers independent of BRCA mutations. Clin Cancer Res. 2018;24:3163-3175.

70. Karakashev S, Fukumoto T, Zhao B, et al. EZH2 inhibition sensitizes CARM1-high, homologous recombination proficient ovarian cancers to PARP inhibition. Cancer Cell. 2020;37:157-167.e6.

71. Flynn RL, Zou L. ATR: a master conductor of cellular responses to DNA replication stress. Trends Biochem Sci. 2011;36:133-140.

72. Jin MH, Oh DY. ATM in DNA repair in cancer. Pharmacol Ther. 2019;203:107391.

73. Smith J, Tho LM, Xu N, et al. The ATM-Chk2 and ATR-Chk1 pathways in DNA damage signaling and cancer. Adv Cancer Res. 2010;108:73-112.

74. Curtin NJ. DNA repair dysregulation from cancer driver to therapeutic target. Nat Rev Cancer. 2012;12:801-817.

75. Shrivastav M, De Haro LP, Nickoloff JA. Regulation of DNA double-strand break repair pathway choice. Cell Res. 2008;18:134-147.

76. Choi M, Kipps T, Kurzrock R. ATM mutations in cancer: therapeutic implications. Mol Cancer Ther. 2016;15:1781-1791.

77. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474:609-615.

78. Weber AM, Drobnitzky N, Devery AM, et al. Phenotypic consequences of somatic mutations in the ataxia-telangiectasia mutated gene in non-small cell lung cancer. Oncotarget. 2016;7:60807-60822.

79. Batey MA, Zhao Y, Kyle S, et al. Preclinical evaluation of a novel ATM inhibitor, KU59403, in vitro and in vivo in p53 functional and dysfunctional models of human cancer. Mol Cancer Ther. 2013;12:959-967.

80. Hickson I, Zhao Y, Richardson CJ, et al. Identification and characterization of a novel and specific inhibitor of the ataxia-telangiectasia mutated kinase ATM. Cancer Res. 2004;64:9152-9159.

81. Mak JPY, Ma HT, Poon RYC. Synergism between ATM and PARP1 inhibition involves DNA damage and abrogating the G_2 DNA damage checkpoint. Mol Cancer Ther. 2020;19:123-134.

82. Mei L, Zhang J, He K, Zhang J. Ataxia telangiectasia and Rad3-related inhibitors and cancer therapy: where we stand. J Hematol Oncol. 2019;12:43.

83. Schmitt A, Knittel G, Welcker D, et al. *ATM* deficiency is associated with sensitivity to PARP1- and ATR inhibitors in lung adenocarcinoma. Cancer Res. 2017; 77:3040-3056.

84. Durant ST, Zheng L, Wang Y, et al. The brain-penetrant clinical ATM inhibitor AZD1390 radiosensitizes and improves survival of preclinical brain tumor models. Sci Adv. 2018;4:eaat1719.

85. Riches LC, Trinidad AG, Hughes G, et al. Pharmacology of the ATM inhibitor AZD0156: potentiation of irradiation and olaparib responses pre-clinically. Mol Cancer Ther. 2020;19:13-25.

86. Bartkova J, Horejsí Z, Koed K, et al. DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. Nature. 2005;434:864-870.

87. Lee KY, Chung KY, Koo HS. The involvement of FANCM, FANCI, and checkpoint proteins in the interstrand DNA crosslink repair pathway is conserved in C. elegans. DNA Repair (Amst). 2010;9:374-382.

88. Patil M, Pabla N, Dong Z. Checkpoint kinase 1 in DNA damage response and cell cycle regulation. Cell Mol Life Sci. 2013;70:4009-40021.

89. Gorgoulis VG, Vassiliou LV, Karakaidos P, et al. Activation of the DNA damage checkpoint and genomic instability in human precancerous lesions. Nature. 2005; 434:907-913.

90. Reaper PM, Griffiths MR, Long JM, et al. Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR. Nat Chem Biol. 2011;7:428-430.

91. Enders GH. Gauchos and ochos: a Wee1-Cdk tango regulating mitotic entry. Cell Div. 2010;5:12.

92. Lee J, Kumagai A, Dunphy WG. Positive regulation of Wee1 by Chk1 and 14-3-3 proteins. Mol Biol Cell. 2001;12:551-563.

93. O'Connell MJ, Raleigh JM, Verkade HM, Nurse P. Chk1 is a wee1 kinase in the G2 DNA damage checkpoint inhibiting cdc2 by Y15 phosphorylation. EMBO J. 1997;16:545-554.

94. Hill SJ, Decker B, Roberts EA, Horowitz NS, et al. Prediction of DNA repair inhibitor response in short-term patient-derived ovarian cancer organoids. Cancer Discovery. 2018;8:1404-1421.

95. Parmar K, Kochupurakkal BS, Lazaro JB, et al. The CHK1 inhibitor prexasertib exhibits monotherapy activity in high-grade serous ovarian cancer models and sensitizes to PARP inhibition. Clin Cancer Res. 2019;25:6127-6140.

96. Young LA, O'Connor LO, de Renty C, et al. Differential activity of ATR and WEE1 inhibitors in a highly sensitive subpopulation of DLBCL linked to replication stress. Cancer Res. 2019;79:3762-3775.

97. Cerami E, Gao J, Dogrusoz U, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discovery. 2012;2:401-404.

98. Ceccaldi R, O'Connor KW, Mouw KW, et al. A unique subset of epithelial ovarian cancers with platinum sensitivity and PARP inhibitor resistance. Cancer Res. 2015;75:628-634.

99. Mouw KW, D'Andrea AD, Konstantinopoulos PA. Nucleotide excision repair (NER) alterations as evolving biomarkers and therapeutic targets in epithelial cancers. Oncoscience. 2015;2:942-943.

100. Huntoon CJ, Flatten KS, Wahner Hendrickson AE, et al. ATR inhibition broadly sensitizes ovarian cancer cells to chemotherapy independent of BRCA status. Cancer Res. 2013;73:3683-3691.

101. Josse R, Martin SE, Guha R, et al. ATR inhibitors VE-821 and VX-970 sensitize cancer cells to topoisomerase i inhibitors by disabling DNA replication initiation and fork elongation responses. Cancer Res. 2014;74:6968-6979.

102. Thomas A, Redon CE, Sciuto L, et al. Phase I study of ATR inhibitor M6620 in combination with topotecan in patients with advanced solid tumors. J Clin Oncol. 2018;36:1594-1602.

103. Zou L. Ataxia telangiectasia-mutated and Rad3-related inhibition and topoisomerase I trapping create a synthetic lethality in cancer cells. J Clin Oncol. 2018; 36:1628-1630.

104. Angius G, Tomao S, Stati V, et al. Prexasertib, a checkpoint kinase inhibitor: from preclinical data to clinical development. Cancer Chemother Pharmacol. 2020; 85:9-20.

105. Lowery CD, Dowless M, Renschler M,B et al. Broad spectrum activity of the checkpoint kinase 1 inhibitor prexasertib as a single agent or chemopotentiator across a range of preclinical pediatric tumor models. Clin Cancer Res. 2019;25:2278-2289.

106. Mani C, Jonnalagadda S, Lingareddy J, et al. Prexasertib treatment induces homologous recombination deficiency and synergizes with olaparib in triple-negative breast cancer cells. Breast Cancer Res. 2019;21:104.

107. Morimoto Y, Takada K, Takeuchi O, et al. Prexasertib increases the sensitivity of pancreatic cancer cells to gemcitabine and S-1. Oncol Rep. 2020;43:689-699.

108. D'Andrea AD. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst). 2018;71:172-176.

109. Yazinski SA, Comaills V, Buisson R, et al. ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells. Genes Dev. 2017;31:318-332.

110. Jin J, Fang H, Yang F, et al. Combined inhibition of ATR and WEE1 as a novel therapeutic strategy in triple-negative breast cancer. Neoplasia. 2018;20:478-488.

111. Qi W, Xu X, Wang M, et al. Inhibition of Wee1 sensitizes AML cells to ATR inhibitor VE-822-induced DNA damage and apoptosis. Biochem Pharmacol. 2019; 164:273-282.

112. Mouw KW, Konstantinopoulos PA. From checkpoint to checkpoint: DNA damage ATR/Chk1 checkpoint signalling elicits PD-L1 immune checkpoint activation. Br J Cancer. 2018;118:933-935.

113. Montano R, Chung I, Garner KM, et al. Preclinical development of the novel Chk1 inhibitor SCH900776 in combination with DNA-damaging agents and antimetabolites. Mol Cancer Ther. 2012;11:427-438.

114. Lee JM, Nair J, Zimmer A, et al. Prexasertib, a cell cycle checkpoint kinase 1 and 2 inhibitor, in BRCA wild-type recurrent high-grade serous ovarian cancer: a first-in-class proof-of-concept phase 2 study. Lancet Oncol. 2018;19:207-215.

115. Lheureux S, Cabanero M, Cristea MC, et al. A randomized double-blind placebo-controlled phase II trial comparing gemcitabine monotherapy to gemcitabine in combination with adavosertib in women with recurrent, platinum resistant epithelial ovarian cancer: a trial of the Princess Margaret, California, Chicago and Mayo Phase II Consortia. J Clin Oncol. 2019;37 (suppl; abstr 5518).

116. Oza AM, Weberpals JI, Provencher DM, et al. An international, biomarker-directed, randomized, phase II trial of AZD1775 plus paclitaxel and carboplatin (P/C) for the treatment of women with platinum-sensitive, TP53-mutant ovarian cancer. J Clin Oncol. 2015;33 (suppl; abstr 5506).

117. Leijen S, van Geel RM, Sonke GS, et al. Phase II study of WEE1 inhibitor AZD1775 plus carboplatin in patients with TP53-mutated ovarian cancer refractory or resistant to first-line therapy within 3 months. J Clin Oncol. 2016;34:4354-4361.

118. Konstantinopoulos P, Hendrickson A, Penson R, et al. LBA60: Randomized phase II (RP2) study of ATR inhibitor M6620 in combination with gemcitabine versus gemcitabine alone in platinum-resistant high grade serous ovarian cancer (HGSOC). Ann Oncol. 2019;30 (Suppl 5; abstr v897).