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Strategies in Overcoming Homologous Recombination Proficiency and PARP Inhibitor Resistance

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Abstract

Ovarian cancer is the second most common gynecologic malignancy in the United States and the most common cause of gynecologic cancer–related death. The majority of ovarian cancers ultimately recur despite excellent response rates to upfront platinum- and taxane-based chemotherapy. Maintenance therapy after frontline treatment has emerged in recent years as an effective tool for extending the platinum-free interval of these patients. Maintenance therapy with PARP inhibitors (PARPis), in particular, has become part of standard of care in the upfront setting and in patients with platinum-sensitive disease. Homologous recombination deficient (HRD) tumors have a nonfunctioning homologous recombination repair (HRR) pathway and respond well to PARPis, which takes advantage of synthetic lethality by concomitantly impairing DNA repair mechanisms. Conversely, patients with a functioning HRR pathway, that is, HR-proficient tumors, can still elicit benefit from PARPi, but the efficacy is not as remarkable as what is seen in HRD tumors. PARPis are ineffective in some patients due to HR proficiency, which is either inherent to the tumor or potentially acquired as a method of therapeutic resistance. This review seeks to outline current strategies employed by clinicians and scientists to overcome PARPi resistance—either acquired or inherent to the tumor.

Introduction

Gynecologic malignancies are among the leading cause of cancer-related death in women in the United States, and ovarian cancer is the deadliest. The American Cancer Society predicts that more than 21,000 women will be diagnosed with ovarian cancer in 2020 in the United States, and approximately 14,000 women will die from their disease (1). Historically, patients with high-grade serous ovarian cancer (HGSOC) have been treated with a combination of surgical cytoreduction with platinum- and/or taxane-based chemotherapy. Despite promising initial responses to therapy that include complete responses, approximately 80% of women experience disease progression or recurrence

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(2). For this reason, further research into superior treatment options for these patients is necessary.

PARP proteins are involved in the repair of both single- and double-stranded DNA breaks (SSB and DSB) through several repair pathways, including mismatch repair, nonhomologous end joining, and nucleotide excision repair (3). Notably, PARP proteins are integral to base excision repair in which a single misplaced base is exchanged with the correct base (Fig. 1). In cells with a nonfunctional homologous recombination (HR) repair pathway, PARP-mediated base excision is utilized for cell survival. Inhibiting these pathways via PARP inhibition (PARPi) causes an accumulation of SSBs that eventually stall replication forks and prohibit replication, causing an accumulation of DSBs. The failed repair of DSBs due to HRD can result in insurmountable DNA damage that ultimately leads to cancer cell death. (4). HRD can arise from mutations in the tumor suppressor genes *BRCA1/2*, and other genes involved in the HRR pathway, including *ATM*, *CHEK2*, *BRIP1*, *RAD51C*, and *PALB2*.

Once it was discovered that cells with mutations in *BRCA1/2* had increased sensitivity to PARPis, (5), the concept of synthetic lethality quickly became the focus of many preclinical and clinical studies. Synthetic lethality occurs when cells that are genetically predisposed to the inactivation of one pathway are targeted by the intentional inactivation of a second pathway, whereas the inactivation of either pathway alone would not be enough to kill the cell (6). The SOLO1 trial (NCT01844986) led to the FDA approval of a PARPi, olaparib, for upfront maintenance therapy in patients with the BRCA mutation and demonstrated an unprecedented improvement in progression-free survival (PFS) of 36 months compared with placebo (7). Similarly, the SOLO2 trial evaluated the use of maintenance olaparib in recurrent, platinum-sensitive, *BRCA1/2*-mutated ovarian cancers and demonstrated an improvement of PFS in the olaparib group. The recently published SOLO2 data showed a benefit of 13 months in overall survival (OS), further proving the efficacy of maintenance PARPi in this patient population (8). In addition, niraparib maintenance therapy has now been approved in the frontline setting regardless of BRCA or HR status based on the PRIMA trial (NCT02655016), although the magnitude of benefit is not as great in the HR-proficient (HRP) population (9). Three PARPis (niraparib, olaparib, and rucaparib) are currently approved for use in the maintenance setting of treatment for platinum-sensitive HGSOC.

Mechanisms of PARPi Resistance

Despite the revolutionary impact of PARPis on the HRD population, PARPi resistance (PIR) has been observed in many patients (10). Among those mechanisms of resistance studied includes the upregulation of drug efflux pumps such as P-glycoprotein. This upregulation was seen after treatment of *BRCA-1*–deficient breast cancer cells in mice that developed PARPi resistance (11). This mechanism of resistance through drug efflux is also a commonly described mechanism of resistance to platinum-based chemotherapy through a variety of transporters including CTR1, CTR2, ATP7A, and ATP7B (12).

The vast majority of PIR mechanisms revolve around the restoration of HRR in cells that are deficient. Previous studies have shown that the restoration of patients with

wild-type *BRCA1/2* (wt*BRCA*) phenotypein whose tumors harbor *BRCA1/2* mutations—either through secondary mutations or epigenetic modifications—can cause significant PIR (13, 14). One study showed that nearly 50% of patients with platinum-resistant ovarian carcinomas had a secondary mutation that restored the *wt-BRCA* gene and thus HR function (13). Other HR gene mutations have been shown to be reversed by secondary mutations, including *PALB2*, *RAD51C*, and *RAD51D*. In fact, this mechanism of resistance via restoration of HR has been shown to play a role in the resistance of ovarian cancer cells to platinum-based chemotherapy as well (15). Particular sensitivity of ovarian cancer cells with HRD to platinum-based chemotherapy has been described, as it allows for the accumulation of DNA DSBs that are rendered irreparable by the lack of HR functionality. Subsequently, the theoretical resistance to platinum-based therapy as a result of regaining HR function has been proven true as seen by BRCA reversion mutations in patients with platinum-resistant ovarian cancer (16). This overlap in resistance allows for the further evasion of HGSOC from advanced therapy.

An additional mechanism of PIR that has been described is the rewiring of HRR and the DNA damage response by replication fork protection. HR proteins such as BRCA1/2 function to prevent replication fork stress and therefore protect genomic stability (17). Resistant cells have been shown to bypass the loss of fork protection through mechanisms like the downregulation of MRE11 or loss of CDH4 (18). Because restoring replication fork protection is independent of DNA repair, combination therapy targeting this mechanism could result in synergistic lethality with PARPis.

Downregulation of PARP1 proteins is another classically described mechanism of PIR. During PARPi treatment, the cytotoxicity that occurs as a result of PARP1-trapped DNA complexes can lead to a depletion of PARP protein expression rather than cell death (19). Moreover, a clinical case of PIR has been seen as a result of a *PARP1* mutation (20). The loss of PARP1 protein in cancer cells was only found in patients with either some or all of the functioning HR pathway. Thus, it can be conferred that patients with complete loss of HR do not show this mechanism of PARPi resistance.

According to The Cancer Genome Atlas, approximately half of ovarian cancers are considered to be HRP (21). In addition, PIR occurs in more than 50% of patients with ovarian cancer, which poses a question of how clinicians can overcome both acquired and *de novo* HRP. These tumors have an overall worse response to platinum-based chemotherapy and dismal survival outcomes, as shown by a worse OS in wt*BRCA* cases compared with *BRCA*-mutated cases (median OS, ~40 vs. ~60 months, respectively; ref. 22). Because of the unmet need to improve outcomes in patients with HRP, many studies are actively trying to better understand ways to “switch” an HRP tumor to have an HRD phenotype. This review focuses on research regarding the utilization of various targeted agents (Tables 1 and 2) to sensitize HRP ovarian cancers to PARPis or resensitize patients with HRD that have become resistant to PARPis.

ATR Inhibitors

Historically, ataxia telangiectasia Rad3-related (ATR) is known to be a major regulator of a cell-cycle checkpoint signaling pathway controlled by checkpoint kinase 1 (Chk1). This

pathway functions during the G_2–M phase of the cell cycle to recognize DNA irregularities and induce cell-cycle arrest for DNA repair (23). Beyond its role in the Chk1 pathway of DNA repair, ATR has also been implicated as a regulator of several proteins in the HRR pathway, including activation of BRCA1, PALB2, and RAD51, which suggests the potential for mechanistic synergism between ATR inhibitors (ATRis) and PARPis (24). In fact, the use of ATRis has been shown to sensitize both HRP and HRD ovarian cancer cells to the use of PARPis in preclinical models (25). Several clinical trials have explored this combination treatment, including an ongoing phase I trial investigating the combination therapy of cisplatin, veliparib, and VX-970 (ATRis) in the treatment of refractory solid tumors (NCT02723864).

ATRis have also been found to impair replication fork protection, a known mechanism of PIR. They target this mechanism by inhibiting Rad51-loading onto stalled replication forks in HRD cells, subsequently subjecting the cell to synthetic lethality induced by PARPi (26). The ATRi VE-821 has been shown to enhance the degradation of stalled replication forks using *ex vivo* DNA fiber analyses. Unfortunately, this effect was not seen in cells with wtBRCA proteins, showing that the use of ATRis may not extend to innately HRP tumors (27).

Previous studies have demonstrated a relationship between PARPi response and the expression of SLFN11, a gene involved in cell-lethal replication inhibition (28). By prolonging cell-cycle arrest and inducing replication fork damage, high *SLFN11* expression can cause hypersensitivity to PARPis (29). PIR was further demonstrated after the *SLFN11* gene was inactivated in preclinical models (28). These cells were no longer able to go through PARP trapping at prolonged cell arrest points and thereafter increased the reliance on ATR checkpoints to promote cell survival (28). Using these data as a foundation, ATRis could be of particular use for PARPi sensitization in cancer cells with PIR.

PI3K Inhibitors

The PI3K pathway has been heavily investigated given its multiple roles in cancer progression. Aberrations in this pathway can contribute to both the initial development and the survival of ovarian cancer cells, providing an opportunity for targeted therapies. Despite this, there has been minimal clinical benefit seen when treating patients with epithelial ovarian cancer (EOC) with single-agent PI3K inhibitors (PI3Kis; ref. 30). In contrast, there is an abundance of preclinical data supporting the synergism between PARPis and PI3Kis as PI3Kis can increase the antimetabolic effects of PARPis (31). One study showed that PI3Kis caused the cessation of DNA synthesis as well as cytoskeletal functions, processes that are further exacerbated by PARPis. Utilizing mouse models of mammary epithelial cells, treatment with PARPis + PI3Kis resulted in a decrease in S-phase cell-cycle progression due to impairment of nucleotide synthesis (32).

When considering the combinational use of PARPis and PI3Kis in the treatment of ovarian cancer, the cross-talk of the PI3K and HRR pathways must be taken into account. Beyond its mechanisms of cell-cycle regulation and metabolic influence, PI3K helps control the repair of DSBs by acting as a sensor of genomic instability and detecting DSBs (33). One preclinical study showed that PI3Kis resulted in the downregulation of *BRCA1/2* and

induced an HRD phenotype in the cell (34). In addition, a phase Ib study published in 2019 showed that combining the PI3Kis alpelisib with olaparib in recurrent HGSOC was safe; and potential efficacy was seen with an overall response rate of 33% (35). Currently, there is a phase I clinical trial (NCT01623349) examining the oral PI3Kis, BKM120, and BYL719, in conjunction with olaparib in patients with HGSOC and triple-negative breast cancer (TNBC). Preliminary data from this trial have shown a 29% response rate in patients with wt*BRCA1/2* tumors regardless of platinum sensitivity, recommending phase II studies to further examine this relationship (31). The current data fully support continued investigation of the clinical synergism between PI3Kis and PARPis.

Glutaminase Inhibitors

The metabolic alterations in tumor cells have been thoroughly investigated, with particular focus on the adjustments that tumor cells make to enable their survival in hypoxic conditions. It has been demonstrated that cancer cells have a decreased ability for glucose to enter the tricarboxylic acid cycle, which results in reliance on other carbon sources for the cell, including glutamine (36). This shift toward using glutamine is an integral part of the development and progression of invasive and advanced ovarian cancer.

Previous data have shown that inhibition of glutaminase can cause an arrest in the growth of HGSOC (37). When exploring this mechanism as a potential cancer therapeutic target, one must consider the role of phosphate-activated mitochondrial glutaminase (GLS1), a key enzyme involved in glutamine metabolism that allows the conversion of glutamine to glutamate (38). A study investigating the effects of the GLS1 inhibitor compound 968 found that glutaminase inhibition caused cessation of ovarian cancer cell proliferation and reduced the glutamine metabolism for the sustainment of cancer cells (39). This inhibitor also increased reactive oxygen species formation, cell apoptosis, and induced cell-cycle arrest leading to tumor cell destruction. The use of glutaminase inhibitors to sensitize ovarian cancer to PARPis is still being explored. Glutamine is a necessary nitrogen source for nucleotide synthesis and subsequent DNA synthesis. Thus, by inhibiting the metabolism of glutamine, the cell would experience a depletion of completed nucleotides and would be unable to repair DNA effectively (40). This buildup of DNA replication stress an thereafter be exploited by PARPis in cancer cells. Okazaki and colleagues found synergism between glutaminase inhibitors and PARPis in the treatment of renal cell carcinoma due to von Hippel-Lindau disease (41). Currently, a phase I/II clinical trial is investigating the results of treating metastatic solid tumors with a combination of the glutaminase inhibitor, CB-839, and PARPi, talazoparib (NCT03875313). In addition, an upcoming investigator-initiated clinical trial at our institution will explore the efficacy of combining CB-839 with niraparib in the treatment of platinum resistant, wt*BRCA1/2* ovarian cancer (NCT03944902). This could provide insight as to possible mechanism of overcoming HRP, although more research exploring the potential to reverse this phenotype with glutaminase inhibitors is warranted.

HDAC Inhibitors

HDAC class I expression is prevalent in ovarian cancers and has been examined as a potential cause of resistance to platinum-based chemotherapy (42). HDAC expression in HGSOC is associated with a poor prognosis and provides an opportunity for targeted

pharmacotherapy. HDAC inhibitors (HDACis) have been shown to downregulate the transcription of wild-type HRR genes such as *RAD51*, leading to a further increase of irreparable DNA damage and providing an opportunity for combination treatment with PARPis (43).

The HDACi romidepsin has been shown to enhance the antitumor effects of cisplatin by further inflicting DNA damage (44). In a study using the HDACi sodium butyrate, tumor radiosensitivity was enhanced because of the DNA damage caused by downregulation of HRR genes (43). This theory was further explored by Konstantinopoulos and colleagues, who showed through preclinical microarray assays that vorinostat, also known as suberanilohydroxamic acid, induced the downregulation of critical HRR genes *RAD51* and *BRCA* (45). Currently, there is a phase I clinical trial underway looking at the combinational treatment of olaparib with vorinostat in the treatment of metastatic breast cancer (NCT03742245). Future work could explore this combination therapy in patients with *wtBRCA* or *BRCA*-mutated ovarian cancer resistant to PARPi therapy.

Immune Checkpoint Inhibitors

The response of HGSOC to immune checkpoint modulators has been variable, usually seen only in patients with high microsatellite instability (46). For this reason, other agents such as PARPis have been explored to be used in conjunction with immunotherapy in the treatment of HGSOC. It has previously been demonstrated that HRD tumors are more sensitive to immune checkpoint blockade (ICB) therapies than HRP tumors (47). In a preclinical study investigating the efficacy of treating ovarian cancer cells with a PARPi prior to the use of ICB therapy, combining niraparib with full dose anti–PD-1 resulted in significant tumor growth inhibition compared with either drug used alone (48). Although preclinical studies strongly suggest that the use of PARPis and ICB therapy is of clinical benefit in patients with HRD, the utility was not demonstrated in patients with HRP (47).

A single-arm phase I/II clinical trial (NCT02657889) investigating the clinical response of patients with HGSOC to both PARPis and ICB therapy using pembrolizumab demonstrated promising antitumor activity. In fact, even patients with a functioning HR pathway had higher antitumor activity than those treated with monotherapy niraparib or pembrolizumab (49). These findings suggest the potential for clinical combination of ICB therapies and PARPis in the setting of HRP.

VEGFR and EGFR Inhibitors

The VEGF protein family consists of growth factors that promote increased vascularity and angiogenesis in response to hypoxic conditions. VEGF is induced by hypoxia-inducible factors that are upregulated to allow tumors to thrive in a hypoxic environment, which plays a part in several diseases when overexpressed (50). Various agents targeting VEGF have been clinically utilized in several malignancies with the intention of destroying the tumor vascular supply (51).

A phase II clinical trial investigated the combination of olaparib and cediranib, a potent inhibitor of VEGFRs, in the treatment of platinum-resistant ovarian cancers (NCT01116648). The combination treatment resulted in an increase in PFS compared

treatment with olaparib alone (52). Specifically, the added activity of cediranib increased tumor regression even in patients with wt*BRCA1/2*, suggesting that synergism induced by cediranib extends to HRP tumors (52). Despite this, GY004 (NCT02446600), a recent phase III open-label clinical trial that was designed to expand on NCT01116648, showed no significant improvement in the PFS of patients treated with the combination treatment compared with olaparib alone (regardless of HR status). This mechanism could be explained by data showing that VEGFR inhibition in ovarian cancer cells is associated with decreased expression of wt*BRCA1/2* (52).

Furthermore, the EGFR (ERBB/HER) has been shown to be associated with accelerated tumor growth when overexpressed. The use of the EGFR inhibitor neratinib has been shown in preclinical studies to act in synergy with niraparib to accentuate ovarian cell death via exploitation of synthetic lethality to heighten levels of DNA damage (53). This is being further explored in an ongoing phase I/Ib clinical trial utilizing the combination therapy in the treatment of platinum-resistant ovarian cancer (NCT04502602). Overall, the use of EGFR inhibitor therapy in combination with PARPis should be explored further to understand its use in the treatment of HRP ovarian cancers and whether it can overcome that barrier of treatment.

WEE1 Inhibitors

Wee1-like kinase (WEE1) is highly upregulated in certain cancers, including HGSOC, as well as glioblastoma, osteosarcoma, melanoma, and breast and vulvar carcinoma (54). By targeting the G_2–M checkpoint via WEE1 inhibition (WEE1i), tumor cells with dysfunctional G_1–S checkpoints are selectively targeted and ultimately undergo cell death due to irreparable DNA damage (55).

In recent years, WEE1 has been linked to the HRR pathway via its interaction with DNA repair mechanisms, making it an interesting target to study in combination with PARPis. A study using the WEE1i AZD1775 in combination with gemcitabine-radiation in pancreatic cancer cells showed that upon treatment with AZD1775 and chemoradiation, only HRP cells were sensitive to chemoradiation (56).

One proposed mechanism for WEE1's role in HRR is through nucleotide exhaustion and PARP trapping. A previous study investigating the combination AZD1775 with olaparib found that only *KRAS*-mutant non–small cell lung cancer (NSCLC) were more sensitive to radiotherapy than cells treated with either agent alone (57). In addition, through experiments using nucleotide depletion, it was observed that PARP1 trapping must be present for WEE1i to sensitize tumors to radiotherapy. Although PARPis alone can radiosensitize a tumor regardless of PARP1 trapping activity, the current theory for the synergy of WEE1i with PARPis is that the two agents impair DNA replication at multiple timepoints (57). More experiments must be done to further characterize how WEE1i affects the HRR pathway.

BET Inhibitors

Similar to WEE1i, BET inhibitors (BETis) have been increasingly linked to the HRR pathway by synergizing with PARPi via induction of DNA damage (58). The BET family of proteins includes BRD2, BRD3, BRD4, and BRDT, each with a conserved N-terminal

bromodomain. One study has shown that *BRD4* is a necessary factor for survival of ovarian cancer cell lines such as OVCAR8 (59). In addition, it was observed that HGSOC tumors with *BRD4* amplifications may derive the most clinical benefit from BETis (60). This finding is particularly interesting as the *BRD4*-overexpressing subtype often do not harbor *BRCA1/2* mutations, rendering these cancers limited in their treatment options.

BRD4 expression has also been recognized as a component of PIR. In a study investigating aldehyde dehydrogenase (ALDH) expression in ovarian cancer cell lines, cells with acquired resistance to olaparib demonstrated increased activity in ALDH via elevated expression of *ALDH1A1* (61). This increase in *ALDH1A1* expression stems from *BRD4* overexpression, which can be induced by exposure to olaparib. BETis have been shown to suppress the expression of both *WEE1* and *TOPBP*, which sensitized wt*BRCA1/2* cells to a PARPi. In addition, BETi treatment was able to resensitize m*BRCA2* cells with acquired olaparib resistance to PARPis (58). Inhibition of *BRD4* has also been shown to result in inhibition of *ALDH1A1* expression, which assisted in overcoming PIR in HGSOC cells (61).

The BRD4 inhibitor INCB054329 caused decreased activity in both *BRCA1* and *RAD51* as well as HR reporter activity in an HRP ovarian cancer cell line, supporting its ability to induce an HRD phenotype (62). In addition, cell lines treated with the combination of INCB054329 and olaparib showed increased tumor cytotoxicity compared with cells treated with either agent alone (62). A similar study demonstrated that the three BETis: JQ1, I-BET762, and OTX015 were able to sensitize HRP cells to PARPis (63). Cumulatively, these findings suggest that the combination of BET and PARP inhibition warrants further investigation in HRP tumors.

BCL2 Inhibitors

B-cell lymphoma 2 (BCL2) is a group of proteins that are key cell death regulators, making it a potential key player to target cancer cells (64). The expression of *BCL2* genes have been shown to be associated with increased chemotherapy resistance, specifically taxane- and platinum-based therapies (65).

Synergy has been observed between rucaparib and the BCL2 inhibitor navitoclax—the combination therapy induced more apoptosis than navitoclax monotherapy (64). Preferential apoptotic activity was seen in cells with mutations in HRR genes, indicating that cells with a dysfunctional HRR system may rely more heavily on the anti-apoptotic BCL group of proteins. Furthermore, Stover and colleagues demonstrated the effectiveness of BCL2 inhibition in sensitizing HGSOC cells to PARPis (65). Finally, the use of combination therapy with navitoclax and talazoparib in the treatment of three *wt-BRCA* HGSOC cell lines showed a greater cytotoxic effect than seen with monotherapy, suggesting a potential clinical benefit in HRP tumors (66).

Currently, an ongoing phase II clinical trial (NCT02591095) is seeking to determine survival of patients with platinum-resistant/refractory ovarian cancer while treated with single-agent use of the BCL2 inhibitor ABT263. Further clinical trials are warranted investigating the clinical use of combinational therapy with BCL2 inhibitors and PARPis in the treatment of ovarian cancer.

CDK1 Inhibitors

Cyclin-dependent kinase 1 (CDK1) is a key cell-cycle regulator; its function is essential for cell proliferation (67). It forms a complex with cyclins to regulate G_1–S phase gene transcription, ultimately promoting cell-cycle progression through the phosphorylation of cell-cycle regulators. It has previously been demonstrated that CDK1 modulates the BRCA1 protein, and a preclinical study demonstrated the cessation of S-phase checkpoint activation due to short hairpin RNA-mediated CDK1 depletion in TNBC (68). This inhibition causes a decrease in the phosphorylation of cell-cycle regulator, BRCA1, resulting in the inhibition of BRCA1-mediated foci formation at sites of DNA damage (68). By disrupting BRCA1 function, it was theorized that CDK1 could inhibit not only cell-cycle checkpoints, but other critical DNA damage repair pathways as well.

This theory was later investigated in a study, which found that decreased CDK1-mediated BRCA1 phosphorylation was able to inhibit the HRR pathway (69). Furthermore, CDK1 inhibition (CDK1i) resulted in an 80% decrease in RAD51 foci formation in an *in vitro* lung adenocarcinoma model. RAD51 function plays a critical role in the HRR pathway, and its decreased expression is associated with *BRCA1*-deficient cells (69). These data demonstrated that CDK1i could inflict similar damage to both wt*BRCA1/2* and m*BRCA1/2* cells, and therefore leaving the cells susceptible to PARPi. As such, combining a PARPi with a CDK1i, such as dinaciclib, could induce synthetic lethality within HRP tumors.

An ongoing phase I trial combining dinaciclib and veriparib in the treatment of advanced solid tumors (NCT01434316) is investigating both *wtBRCA* and *BRCA*-mutated tumors to determine their sensitivity to PARPis with and without a CDK1i. More preclinical and clinical data are needed to determine the effect on PARPi sensitization using dinaciclib in patients with HGSOC with and without functioning HRR.

HSP90 Inhibitors

Mutated BRCA proteins can cause defective protein folding, leading to an unstable secondary structure that ultimately subjects the protein to degradation. HSP90 is a chaperone protein responsible for the stabilization of proteins against this very mechanism. The stabilization of m*BRCA* proteins via HSP90 can result in enhanced RAD51 loading onto stalled replication forks that bypass the HRR pathway (70). The interaction of HSP90 with BRCA proteins as a mechanism of PIR has been a recent focus of investigation in cancer therapeutics.

Beyond the potential for HSP90 inhibitors (HSP90is) to reverse acquired PIR in HRD tumors, preclinical studies have shown that this could be applied even to HRP cells. In a study exposing HRP breast cancer cells to the HSP90i 17-AAG, treatment resulted in decreased activity of the HRR pathway, ATM serine/threonine kinase, and Fanconi anemia DNA repair pathways (71). Treatment with 17-AAG also downregulated wtBRCA1 and RAD51 levels, thus inducing an HRD state in initially HRP cancer cells. Most remarkably, the exposure of 17-AAG to HRP EOC cells sensitized the cells to olaparib- and platinum-based chemotherapy, as measured by DNA damage using a γH2AX assay measurement

(71). This sensitization was not seen in EOC cells with HRD, suggesting a combination of PARPi and HSP90i could be explored clinically within patients with HRP HGSOC.

Conclusion

Targeting the HRR pathway in ovarian cancer through PARPis has been a paradigm-shifting treatment strategy over the past decade. However, approximately half of patients have a limited response to PARPis due to HRP. Therefore, there has been a focus of research in the last decade as to whether innate or acquired HRP can be overcome to induce PARPi sensitivity. Various agents have shown promise in this area either by working synergistically with PARPis or by targeting the HRR pathway through an alternate strategy, both of which have potential clinical benefit in patients with otherwise limited options. The pharmacotherapies mentioned in this review are currently under preclinical or clinical investigation for use in combinational treatment with PARPis to improve response rates and survival outcomes. A variety of clinical trials across the country have the goal of maximizing clinical benefit from PARPis and helping to overcome or prevent therapeutic resistance. Genetic and molecular data are rapidly being integrated into cancer care. These analyses have immense potential to improve patient outcomes by providing more targeted treatments that can be used in combination with PARPis. As the scientific and clinical communities continue to better understand the underlying genetics of the disease and how to manipulate mechanisms that repair DNA damage, we are optimistic that these approaches will ultimately improve the survival of women with ovarian cancer.

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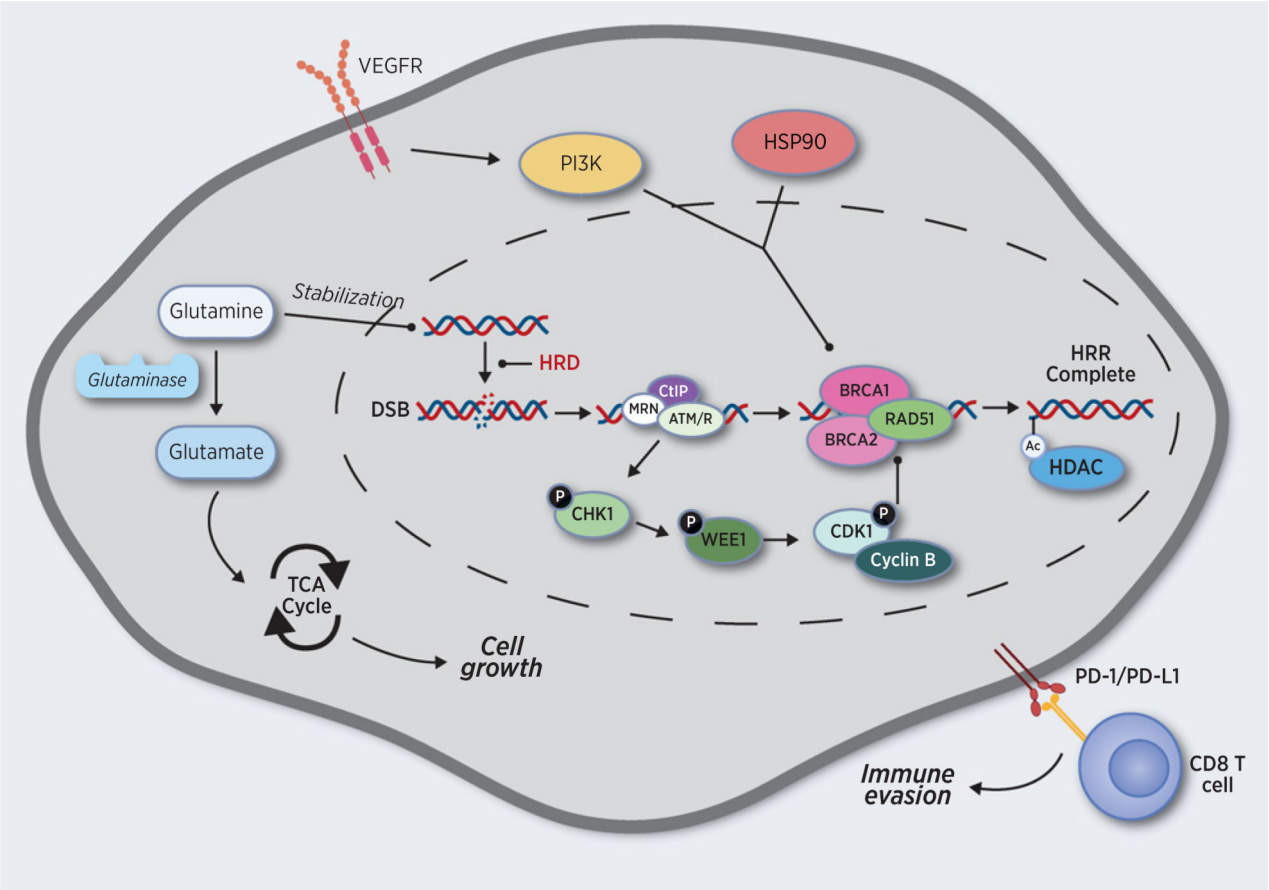

Figure 1.
Overview of the cellular mechanisms that may be targeted to overcome HR proficiency.

Table 1.

Summary of preclinical studies utilizing PARPi combinational therapy.

Drug mechanism	First author, year	Drugs used	Model	Summary of results
ATR inhibitors	Yazinski et al., 2017	Olaparib + VE-821, AZ-20	*mBRCA1*	Disruption of resistance mechanisms and overcoming of resistance to PARPis
	Kim et al., 2020	Olaparib + AZD6738	*mBRCA1* cells, *mBRCA2* PDX	Increased survival of PARPi-resistant cells
PI3K inhibitors	Wang et al., 2016	Olaparib + BKM120	*mBRCA2* OVCA433; *mBRCA1* OVCAR8; *wtBRCA1/2* OVCAR5	Attenuation of DNA repair impairment compared with PARPi treatment alone; decreased growth
	Juvekar et al., 2012	Olaparib + BKM120	*mBRCA1* HCC1937	Delay in tumor growth
	Ibrahim et al., 2012	Olaparib + BKM120	MDA-MB-468, MDA-MB-231, HCC70, HCC1143, BT20	Reduction in tumor growth and downregulation of *BRCA* expression
Glutaminase inhibitors	Emberly et al., 2018	Niraparib/talazopraib + CB-839	TNBC, CRC, non-small cell lung carcinoma, ovarian and prostate cancer cells *in vivo*	Enhanced antitumor activity
	Okazaki et al., 2017	Olaparib + GLS1 inhibitors	*VHL*-deficient/ *VHL*-replete UMRC2, UMRC3, RCC4, UOK102	Suppression of tumor cell growth
BET inhibitors	Karakashev et al., 2017	Olaparib + JQ1	*wtBRCA* OVCAR3	Synergistic increase in DNA damage and apoptosis
	Wilson et al., 2018	Olaparib/rucaparib + JQ1/ INB054329/INCB057643	*wtBRCA1* OVCAR3, OVCAR4, SKOV3	Reduced HR activity and sensitized cell to PARPi, DNA damage, and cell death
	Yang et al., 2017	Olaparib + JQ1/I-BET762/OTX015	*wtBRCA* OVCAR10	Impaired transcription of HR genes, sensitized tumors to PARPi
VEGFR inhibitors	Kaplan et al., 2019	Olaparib + cediranib	IGROV1	Downregulation of *BRCA* gene expression
WEE1 inhibitors	Fang et al., 2020	Talazoparib + adavosertib	OVCAR8	Marked tumor regression with combination therapy
	Parsels et al., 2018	Olaparib +AZD1775	Calu-6 and H23 NSCLC	Enhanced radiosensitization seen with combinational therapy
	Ha et al., 2020	Olaparib +AZD1775	MDA-MB-157, MDA-MB-231, MDA-MB-468, HCC1143, BT-549, Hs 578 T	Induced apoptotic cell death with combinational therapy
CDK1 inhibitors	Johnson et al., 2011	Rucaparib + AG024322	MDA-MB-436	Sensitization of cells to PARPi *in vitro*
	Xia et al., 2013	Olaparib + RO3306	MDA-MB-231, HCC1937, SK-BR-3, MCF-7	Decrease in cell growth with combinational therapy
HSP90 inhibitors	Choi et al., 2014	Olaparib + 17-AAG	HR proficient: Hs578T, MCF-7, MDA-MB-157, T47D, MDA-MB-231HR deficient: MBA-MD-436, HCC-1937, UACC3199	Sensitization of HR-proficient cell lines to PARPi
	Gabbasov et al., 2019	Talazoparib + ganetespib	OVCAR3, OC-1, OC-16	Synergistic decrease in ovarian cancer cell viability
	Jiang et al., 2017	ABT-888 + ganetespib	MCF7	Synergistic inhibition of tumor growth

Abbreviation: CRC, colorectal cancer.

Table 2.

Summary of completed or currently active clinical trials utilizing combination PARPi therapy in patients with ovarian cancer.

Drug mechanism	Study phase	NCT ID #	Drugs used	Study status	Results available
ATR inhibitors	Ib	NCT04267939	Niraparib + BAY 1895344	Recruiting	No
	I	NCT04149145	Niraparib + M4344	Not yet recruiting	No
	II	NCT04065269	Olaparib + AZD6738	Recruiting	No
	II	NCT03462342	Olaparib + AZD6738	Recruiting	No
	Ib	NCT02264678	Olaparib + ceralasertib	Recruiting	No
PI3K inhibitors	I	NCT01623349	Olaparib + BKM120 or BYL719	Active, not recruiting	Yes
	I	NCT04586335	Olaparib + CYH33	Recruiting	No
	I	NCT03586661	Niraparib + copanlisib	Recruiting	No
Glutaminase inhibitors	I	NCT03944902	Niraparib + CB-839	Not yet recruiting	No
VEGFR inhibitors	II	NCT02340611	Olaparib + cediranib	Completed	Yes
	I/II	NCT01116648	Olaparib + cediranib	Active, not recruiting	Yes
	III	NCT02446600	Olaparib ± cediranib vs. nonplatinum chemo	Active, not recruiting	No
	III	NCT03278717	Olaparib ± cediranib	Recruiting	No
	II	NCT03326193	Niraparib + bevacizumab	Active, not recruiting	No
	II	NCT02889900	Olaparib + cediranib	Active, not recruiting	Yes
	II	NCT03314740	Olaparib + cediranib vs. paclitaxel	Active, not recruiting	No
	I	NCT02855697	Olaparib ± cediranib	Active, not recruiting	No
	II	NCT03117933	Olaparib ± cediranib vs. paclitaxel	Active, not recruiting	No
	I	NCT02345265	Olaparib + cediranib	Active, not recruiting	No
	I	NCT00989651	Carboplatin + paclitaxel + bevacizumab + veliparib	Active, not recruiting	Yes
	II	NCT04566952	Olaparib + anlotinib	Recruiting	No
WEE1 inhibitors	II	NCT03579316	Adavosertib ± olaparib	Recruiting	No
CDK1 inhibitors	I	NCT01434316	Veliparib + dinaciclib	Recruiting	No
HSP90 inhibitors	II	NCT03783949	Niraparib + ganetespib	Active, not recruiting	No
	I	NCT02898207	Olaparib + onalespib	Active, not recruiting	No