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Homologous recombination proficient subtypes of high-grade serous ovarian cancer: treatment options for a poor prognosis group

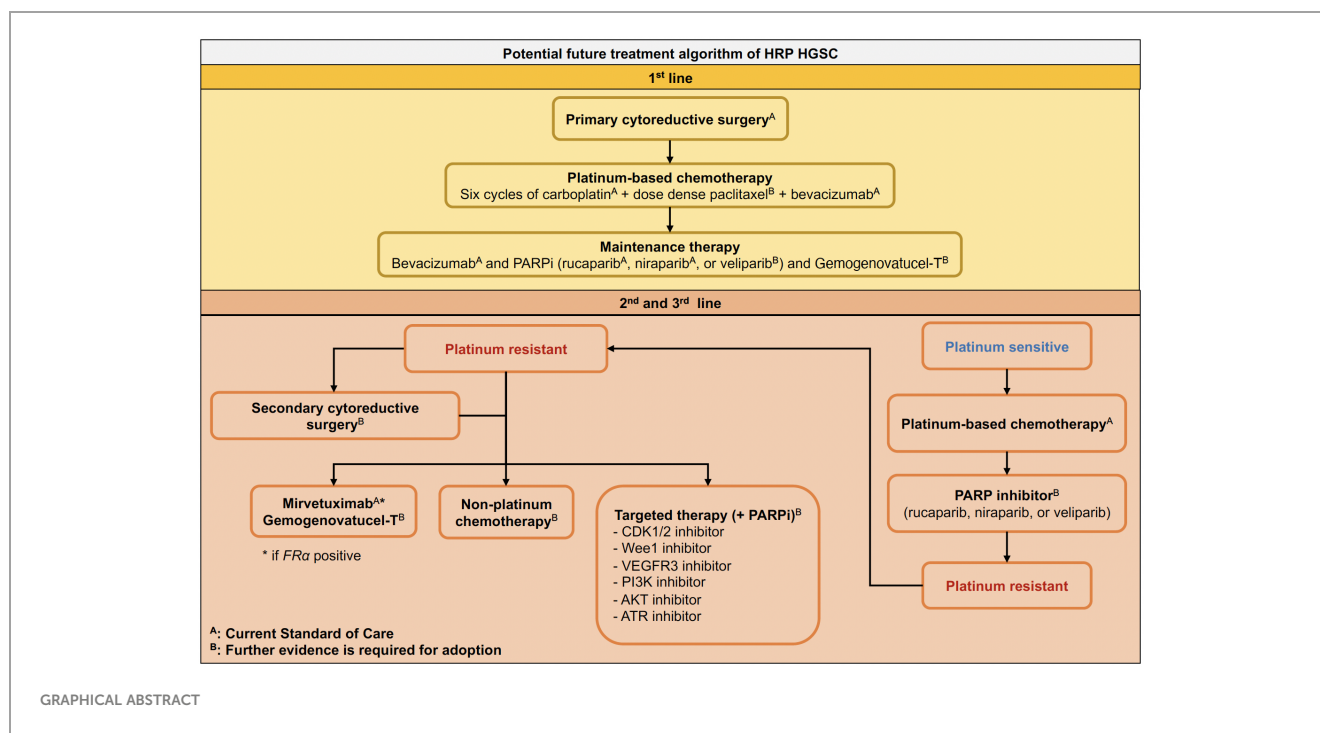
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Approximately 50% of tubo-ovarian high-grade serous carcinomas (HGSCs) have functional homologous recombination-mediated (HR) DNA repair, so-called HR-proficient tumors, which are often associated with primary platinum resistance (relapse within six months after completion of first-line therapy), minimal benefit from poly(ADP-ribose) polymerase (PARP) inhibitors, and shorter survival. HR-proficient tumors comprise multiple molecular subtypes including cases with *CCNE1* amplification, *AKT2* amplification or *CDK12* alteration, and are often characterized as “cold” tumors with fewer infiltrating lymphocytes and decreased expression of PD-1/PD-L1. Several new treatment approaches aim to manipulate these negative prognostic features and render HR-proficient tumors more susceptible to treatment. Alterations in multiple different molecules and pathways in the DNA damage response are driving new drug development to target HR-proficient cancer cells, such as inhibitors of the CDK or P13K/AKT pathways, as well as ATR inhibitors. Treatment combinations with chemotherapy or PARP inhibitors and agents targeting DNA replication stress have shown promising preclinical and clinical results. New approaches in immunotherapy are also being explored, including vaccines or antibody drug conjugates. Many approaches are still in the early stages of development and further clinical trials will determine their clinical relevance. There is a need to include HR-proficient tumors in ovarian cancer trials and to analyze them in a more targeted manner to provide further evidence for their specific therapy, as this will be crucial in improving the overall prognosis of HGSC and ovarian cancer in general.

KEYWORDS

ovarian cancer, homologous recombination proficiency, treatment resistance, PARP inhibitor, CDK inhibitor, PI3K inhibitor, antibody drug conjugate (ADC), vaccine



Introduction

Advanced tubo-ovarian high-grade serous carcinoma (HGSC) accounts for a majority of the disease burden and deaths from ovarian cancer (70–80%) due to its typical late presentation and high 5-year recurrence rate of 75% (1–3). Primary cytoreductive surgery followed by platinum- and taxane-based chemotherapy or neoadjuvant platinum- and taxane-based chemotherapy (NACT) followed by interval cytoreductive surgery is the standard treatment for HGSC (1–9). Most HGSC initially respond well to chemotherapy. However, the majority of patients will experience relapse with treatment resistant disease, particularly those without *BRCA* mutations and without homologous recombination deficiency (HRD) (10–13). Although there has been limited improvement in the 5-year survival rate of most patients over the past three decades (4, 8, 14–16), the introduction of poly(ADP-ribose) polymerase inhibitors (PARPis) as maintenance therapy in HGSC has had a profound impact leading to significant improvements in progression-free survival (PFS) and demonstrating a trend towards improved overall survival (OS), particularly in patients with *BRCA1* or *BRCA2* (*BRCA*) mutations and HRD (1, 3, 13, 17–29).

HRD refers to a loss of homologous recombination-mediated DNA repair (HRR), which is a pathway responsible for the high-fidelity repair of double-stranded DNA breaks that restores the original DNA sequence at the site of damage. HRD contributes to genomic instability and consequently intact HRR plays a role in preventing malignant transformation (30, 31). HRD is caused by inherited or somatic loss of function genetic alterations in well-known driver genes such as *BRCA1* and *BRCA2*, but also by mutations or methylation of other HRR related genes and

potentially other currently undefined mechanisms (32). Patients with HRD HGSC are more likely to benefit from a favorable chemotherapy response, maintenance treatment with PARPis and consequently a longer OS (1, 33–38). However, ~50% of HGSC are HR-proficient (HRP), an established poor prognostic marker associated with primary platinum and PARPi resistance and shorter survival times (36, 39, 40). Platinum-resistant ovarian cancer is defined as disease that relapses within six months of completing first-line treatment, and the probability of a response to platinum re-treatment is less than 10% (33, 41, 42). In fact, HGSC can also progress from HRD to become at least partially HRP by reversion of HR gene alterations through secondary genetic or epigenetic events (43–45). This acquired HR-proficiency is one of the most well described mechanisms of acquired treatment resistance and consequently a major clinical challenge.

HRD status in ovarian cancer is usually inferred by measurement of *BRCA* mutation status and/or the extent of cancer genome scarring associated with loss of HRR genes. Methodologies that assess HRD typically measure the extent of telomeric allelic imbalance, loss of heterozygosity, and large-scale transitions (31, 46). However, these scores are based on permanent genomic scars, thus failing to reflect the current HRD status in the case of HRR restoration (47). An alternative is a dynamic assessment of HR status using functional assays in *ex-vivo* cultures (46). Immunofluorescence microscopy can be used to measure the presence of RAD51 formed molecular complexes which accumulate at sites of double-stranded DNA breaks in HRP cells. By contrast, HRD cells are unable to form RAD51 formed molecular complexes and their absence thus provides a functional indication of a defect in the HR pathway (48, 49). However, such RAD51 assays are yet to be clinically validated.

Additionally, resistance to PARPis may be driven by RAD51-independent mechanisms and consequently cannot be detected by RAD51 assays (50, 51). Current HRD tests vary in the number and type of mutational features assessed, and the optimal thresholds to classify samples as HRD or HRP are not yet well defined. Variation in assays should be considered when evaluating the overall value of such assays in providing prognostic and predictive information.

The heterogeneity of HGSC, including multiple molecular subtypes even within the HRP subgroup, poses a substantial challenge to proper prognostication and clinical management (3, 33, 36, 43, 52, 53). Treatment options for patients with platinum-resistant, non-HRD HGSC are scarce, and the goal of treatment is strongly focused on symptom control and palliation, delaying time to symptomatic progression and improving quality of life (33, 53–57). To date, apart from the antibody-drug conjugate (ADC) mirvetuximab (Elahere[®]), few treatments in addition to cytoreductive surgery and platinum- and taxane-based chemotherapy have shown a survival benefit in this poor prognosis group (3, 33, 42, 53–57).

Recent novel approaches to treat ovarian cancer has largely benefitted patients with HRD HGSC, with or without *BRCA*-alterations (1, 3, 13, 17–29, 58). Further progress in the treatment of HGSC requires approaches that benefit patients with HRP disease, who currently have limited treatment options other than surgery. Here we summarize recent clinical and molecular findings in HRP HGSC and provide an insight into ongoing trials of new potential treatment options.

Characteristics of patients with HR-proficient HGSC

Clinicopathological

Variation in outcomes between patients with HGSC is in part determined by the molecular characteristics of the tumor, with HR-status as one of the important determinants (Table 1). Patients with HRP tumors have an older median age at diagnosis compared to patients with HRD tumors (10, 11, 20, 36). A retrospective analysis of 352 patients showed that HRP tumors required a higher number of cycles of NACT to be considered for interval cytoreductive surgery compared to those with germline *BRCA* mutations and other defects conferring HRD, and less complete gross resection (R0) could be achieved (11). While complete resection in primary and interval cytoreductive surgery remains one of the strongest prognostic features in ovarian cancer (2, 3, 62, 63), the higher number of chemotherapy cycles and lower R0 rate also reflect an inherently resistant tumor (18, 22–24, 26, 33).

Genomic characteristics

Extensive genomic and transcriptomic characterization has provided insight into HGSC with HRR pathway inactivation, most commonly caused by genetic or epigenetic alterations in the

TABLE 1 Clinicopathological characteristics for Non-HRD/HRP versus HRD HGSC.

	Non-HRD/HRP	HRD
Median age (years) (10, 11, 20, 36)	63–64	Germline <i>BRCA</i> +: 54–58.5 Somatic <i>BRCA</i> /HRD+: 58–62
Frequency (%) (10, 11, 36)	~50%	~50%
Non-serous histology subtypes (11)	20%	Germline <i>BRCA</i> +: 6% Somatic <i>BRCA</i> /HRD+: 0%
Molecular characteristics (59–61)	<i>CCNE1</i> -amplification <i>AKT2</i> -amplification Whole genome duplication	<i>BRCA1</i> and <i>BRCA2</i> or other HR genes (<i>BRIPI</i> , <i>PALB2</i> , <i>RAD51C</i> , <i>RAD51D</i>)
Median NACT cycles required (10, 11)	4	Germline <i>BRCA</i> +: 3 Somatic <i>BRCA</i> /HRD+: 3
Rate of complete gross resection (11)	60%	Germline <i>BRCA</i> +: 83% Somatic <i>BRCA</i> /HRD+: 77%
Median progression-free survival (months) (10–13)	5.4–16.9	Germline <i>BRCA</i> +: 23.5–25 Somatic <i>BRCA</i> /HRD+: 20.2–25.2
Median overall survival (months) (11, 17)	40.4–42.3	Germline <i>BRCA</i> +: 68.8 Somatic <i>BRCA</i> /HRD+: 69.2

Adapted from (10–13, 17, 20, 36, 59–61).

NACT, Neoadjuvant Chemotherapy; HRP, Homologous recombination proficient; HRD, Homologous recombination deficient; HR, Homologous recombination.

BRCA genes and alterations in other genes, including *BRIPI*, *PALB2*, *RAD51C*, or *RAD51D*, which encode proteins that are also involved in HR DNA repair (59). By contrast, the molecular drivers of HGSC that have no apparent defects in HR are less well defined (2).

HRP ovarian cancer cells are often characterized by genetic alterations in signaling pathways that contribute to cell cycle dysregulation, such as cyclin E1 (encoded by *CCNE1*) and cyclin dependent kinase (*CDK*) genes (44). Cyclin E1 is an important factor in the G1/S cell cycle transition through its activation of cyclin-dependent kinase 2 (CDK2), allowing the cell to enter the S-phase (64). Besides other cellular mechanisms, limiting the supply of cyclin E1 ensures that the cell remains in the G1 phase by keeping CDK2 inactive until mitogenic signals intervene (65). *CCNE1* expression is dependent on E2F transcription factors that are bound to the retinoblastoma protein (Rb) in an inactivated state when cells are at rest. E2F is released through mitogenic stimuli such as c-MYC which increases the expression of D-type cyclins that in turn combine with CDK4 and CDK6 to phosphorylate and inactivate Rb (65). Furthermore, once activated, the cyclin E1/CDK2 complex is able to phosphorylate Rb and thus upregulate its own expression in the form of a positive feedback loop through the continued release of E2F, independent of mitogenic stimuli (65). Additionally, the cyclin E1/CDK2 complex is an essential component of the chromatin remodeling process required for

DNA replication. Overexpression of cyclin E1 increases the speed at which cancer cells transition from G1 to the S phase (66). This can lead to replicative stress, whole genome duplication, and further promote the dysregulation of genes responsible for proliferation and cell survival, which are also associated with resistance to cytotoxic and targeted therapies (67, 68).

CCNE1 amplification is currently the best characterized driver of HGSC with HR-proficiency. It is important to note, however, that cyclin E1 protein overexpression itself has not been shown to be a predictive biomarker for chemotherapy resistance in epithelial ovarian cancer (EOC), so methods to detect amplification of a gene (e.g. whole-genome sequencing, fluorescence *in situ* hybridization, polymerase chain reaction, single nucleotide polymorphism arrays) are required to identify the *CCNE1* amplified subgroup (69). Approximately 40% of HRP HGSC show an *CCNE1* amplification, which has been shown to be an early event in their development (43, 64). HR pathway gene mutations and *CCNE1* amplification have been shown to be mutually exclusive (44, 60, 65). This suggests that the pathogenesis of HGSC follows at least two distinct pathways, and that *CCNE1*-amplified tumors with cyclin E1 protein overexpression are more likely to be resistant to platinum-based chemotherapy and PARPi due to HR-proficiency (65).

AKT2 amplification is also a poor prognostic marker in EOC (34, 70, 71) and is associated with *CCNE1* amplification (70). The co-amplification of the serine/threonine-protein kinase *AKT2* and *CCNE1* appears to be explained in part by their proximity on chromosome 19q. Pathway analysis indicates that *CCNE1*-amplified cell lines are dependent on multiple genes within the CDK and AKT pathways, suggesting a specific dependence of *CCNE1*-amplified tumors on AKT activity (70). Consequently, combined CDK2 and AKT inhibition may have synergistic anti-tumor activity against *CCNE1*-amplified tumors and hold promise for clinical development (70). It should be noted that although CDK4/6 inhibitors have been investigated in ovarian cancer (72), it is the CDK2 inhibitor which is likely to be effective (73–76).

CDK12-altered HGSC represent a unique subgroup that appear to be HR competent (36). Despite lacking the typical HRD genomic scarring, *CDK12*-altered tumors have a distinct tandem duplication signature and may be more susceptible to chemotherapy and PARPis than other HRP tumors (77). Aside from alterations in *CCNE1*, *AKT2* and *CDK12*, the majority of HRP HGSC remain poorly defined, and integration of genomic, immune, proteomic and functional data is needed for their complete characterization (78–81).

Immune profile

Tumor-infiltrating lymphocytes (TILs) are an established prognostic factor in ovarian cancer, regardless of the extent of surgical cytoreduction and chemotherapy (82–84). The presence of CD8+ TILs in the tumor microenvironment is associated with slower tumor progression, prolonged survival and may be essential for immunotherapy response (84–86). HRD tumors have a significantly increased CD8+/CD4+ ratio of TILs and a higher

number of peritumoral T cells (44). This is likely due to HRD cells accumulating a high number of somatic mutations, which is predicted to result in the expression of more tumor neoantigens that elicit an adaptive immune response and cytotoxic T cell infiltration. These cells are capable of killing cancer cells (84), and in addition to a more favorable response to chemotherapy, explains the improved survival of patients with *BRCA*-mutated ovarian cancer.

By contrast, HRP tumors are characterized by a non-inflamed or “cold” immune phenotype, with fewer CD3+ and CD8+ TILs as well as decreased expression of PD-1 and PD-L1 (87–89). HRP tumors generally have a lower tumor mutational burden due to having intact DNA repair, which, together with a low TIL density, would predict a poor response to immune checkpoint blockade (84). Therefore, HRP tumors may be poor candidates for targeted immunotherapy with PD-1 and PD-L1 inhibitors as recently shown (90–96). Recent approaches to immunotherapy for cold tumors have focused on restoring inflammation by reprogramming myeloid cells, stromal cells, and vascular epithelial cells (97). Additionally, PARPi, low-dose radiotherapy, epigenetic drugs and anti-angiogenesis therapy may enhance T cell infiltration, suggesting their use in combination with vaccines and redirected T-cells using chimeric antigen receptors or bispecific antibodies (84, 98). However, it should be noted that while T cell infiltration and the expression of PD-L1 and other immune checkpoint markers increases following chemotherapy, unlike primary disease, the extent of infiltration does not correlate with patient survival (99, 100).

Treatment options for patients with HRP HGSC

Chemotherapy

Neoadjuvant chemotherapy with interval cytoreductive surgery is currently an alternative for patients with ovarian cancer who have a low chance of initial complete resection and chemosensitive histologic subtypes, or poor health status (1). However, there is a strong correlation between HR-status and response to platinum-based chemotherapy in HGSC; patients with HRP tumors have severely limited responses to chemotherapy, with reported median PFS ranging from 5.4 to 16.9 months (Table 1) (10–13). The chemoresistant nature of HRP tumors highlights the potential benefit of favoring the currently recommended option in HGSC (1) of primary debulking surgery followed by adjuvant platinum and taxane-based chemotherapy in these patients.

An ancillary data analysis of the VELIA/GOG-3005 trial focused on paclitaxel dosing schedule and *BRCA* mutation and HR-status (101). Dose-dense (weekly) paclitaxel was compared to a schedule of every three weeks showing an improved PFS with dose-dense paclitaxel in HRP but not in *BRCA*-mutation or HRD tumors. Previous clinical trials of shorter versus longer paclitaxel intervals in ovarian cancer did not evaluate HR status and therefore further studies are needed to confirm this finding (102, 103). Interestingly, it has been shown that paclitaxel suppresses *CDK1* expression via

decreased *BRCA1* phosphorylation, thereby reducing HR activity in response to DNA damage and increasing sensitivity to PARPi (104), so this combination represents a potential new treatment strategy that needs to be further investigated in HRP HGSC.

HGSC typically involves extensive peritoneal spread and therefore intraperitoneal chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC) have been evaluated in multiple clinical trials. The goal of intraperitoneal chemotherapy is to increase local exposure to the chemotherapeutic agent, and in the case of HIPEC, heated chemotherapy has an additional cytotoxic effect and increases sensitivity to platinum compounds by inducing a transient state of HRD (105). Koole et al. analyzed the effect of HIPEC among patients with ovarian cancer previously enrolled in the phase III OVHIPEC1 trial (105) stratified by *BRCA*-like (HRD) versus non *BRCA*-like (HRP) (106) or *BRCA* mutation status. Although patients with HRD/*BRCA*-wildtype showed a strong benefit in terms of recurrence-free survival (RFS) and a promising trend in OS from HIPEC, this was non-significant in HRP/*BRCA*-wildtype patients and absent in patients with pathogenic *BRCA* mutations, both in terms of RFS and OS (58). It appears that HRP tumors remain resistant to chemotherapy despite hyperthermia. However, there is a lack of long-term survival data for HIPEC, and thus the benefit of this treatment modality remains unclear. The importance of tumor HR status in predicting response and survival following HIPEC may be addressed in ongoing studies (107).

Poly (ADP-ribose) polymerase inhibitors

Maintenance PARPi therapy after first-line treatment and in the platinum sensitive recurrent setting have become standard treatment options in patients with *BRCA*-mutated and HRD EOC (1, 3). PARP is an enzyme that helps repair DNA damage and PARP inhibition causes an accumulation of single- and double-stranded DNA breaks (108). HRD cells are unable to effectively repair the DNA damage, resulting in an accumulation of chromosomal aberrations and cell death (109). As a maintenance therapy PARPi have led to improved PFS and shown a promising trend towards improved OS in EOC, particularly in patients with *BRCA* mutant and/or HRD tumors (17, 18, 20, 21, 23, 24). While the greatest benefit is seen in HRD cancers, an exploratory analysis of the Phase III PRIMA trial showed improvements in PFS with niraparib versus placebo as first-line maintenance monotherapy, regardless of *BRCA* and HR-status (20). Patients with *BRCA*-wildtype/HRP tumors treated with niraparib who responded to first-line chemotherapy had a median PFS of 8.1 months versus 5.4 months for placebo, with an estimated probability of survival at 24 months of 81% in the niraparib group versus 59% in the placebo group. Therefore, niraparib is clinically approved for use in patients with HRP HGSC, with beneficial effects and a manageable tolerability profile (110, 111).

An exploratory analysis of the VELIA/GOG-3005 trial (27) showed that some patients with HRP ovarian cancer and also poor chemosensitivity may have gained a transient, but non-significant benefit from the addition of the PARPi veliparib to carboplatin-

paclitaxel (median PFS 14.7 vs median 6.7 months, HR 0.62, 95% CI 0.37–1.05) (112). The authors of the study hypothesized that veliparib may have induced a chemosensitizing effect on HRP tumors (112, 113). In addition, the Phase III ATHENA-MONO trial demonstrated improved PFS with rucaparib monotherapy compared to placebo in first-line maintenance in patients with newly diagnosed EOC without evidence of HRD (12.1 vs 9.1 months, HR 0.65, 95% CI 0.45–0.95) (13). As a result of such findings, the ESGO-ESMO-ESP consensus guidelines state that niraparib or rucaparib maintenance therapy may be used for patients with HRP HGSC if they have had a complete or partial response to first line chemotherapy or no evidence of disease (1).

Antiangiogenic treatment

Vascular endothelial growth factor (VEGF) promotes increased vascularity and angiogenesis in response to hypoxic conditions and is a key promoter of tumor growth (114). The anti-angiogenic VEGF monoclonal antibody bevacizumab was the first targeted agent to be approved for use in stage III and IV EOC, showing an improved PFS when used in combination with chemotherapy and as maintenance therapy in the first-line setting, however without OS benefit (115, 116). According to the ESGO-ESMO-ESP consensus guidelines, patients with HRP HGSC may receive platinum-based chemotherapy with bevacizumab followed by bevacizumab maintenance as an alternative to the option of maintenance with rucaparib or niraparib (1). Among other mechanisms of action, bevacizumab exposure may trigger HRD by inducing a hypoxic cellular state that can downregulate HR-related genes such as *BRCA1/2* and *RAD51* (117). In addition, the relative benefit of bevacizumab in EOC has been shown to increase as the disease becomes more platinum resistant (118). A retrospective analysis of 124 patients with platinum-sensitive recurrent ovarian cancer showed extended PFS with bevacizumab in patients with cyclin E1 overexpression (median 16.3 vs 7.1 months, $P=0.010$) (118).

Tumor VEGF secretion has been shown to be at least partially responsible for the development and maintenance of ascites, and the AURELIA trial demonstrated that the addition of bevacizumab to chemotherapy improved ascites control. This beneficial effect is certainly relevant for the HRP group as they are more frequently associated with suboptimal debulking, earlier recurrence and ascites (54). Furthermore, the combination of niraparib and bevacizumab evaluated in the pre-specified subgroup analysis of the AVANOVA trial showed a significant improvement in PFS compared to niraparib alone in the HRP population (HR 0.40, 95% CI 0.19–0.85) (119). The Phase III GOG-218 trial also showed prolonged PFS in patients with no HRR gene mutations who received bevacizumab in addition to standard chemotherapy with carboplatin and paclitaxel (HR 0.71, 95% CI 0.60–0.85, $P = 0.0001$). This benefit was not observed in patients with HRR gene mutations (HR 0.95; 95% CI 0.71–1.26) (120). Therefore, the ESMO guidelines recommend that the decision on bevacizumab versus niraparib maintenance in the HRP population should be based on the patient's disease and clinical characteristics, the toxicity profile of the two drug classes, the availability of each drug, and national

guidelines (3, 121). The ongoing Phase I/II MITO 25 trial (NCT03462212) may provide clearer evidence about potential therapy options by comparing whether the carboplatin-paclitaxel-bevacizumab-rucaparib or carboplatin-paclitaxel-rucaparib arms improve PFS compared to standard carboplatin-paclitaxel-bevacizumab in patients with HRP HGSC.

The inhibition of VEGF receptor-3 (VEGFR3) has been shown to decrease *BRCA1* and *BRCA2* expression in ovarian cancer cells and resulted in increased chemosensitivity (122). The randomized Phase II trial (NCT01116648) showed that the combination of olaparib plus cediranib, a VEGF receptor 1/2/3 inhibitor, significantly improved PFS in relapsed platinum-sensitive EOC compared to olaparib alone (median 17.7 months vs 9 months, $P=0.005$), with the greatest benefit in *BRCA*-wildtype patients (HR 0.32, $P=0.008$) (123). These results suggest that there may be greater synergism between the two agents in HRP tumors, with the response to olaparib in HRP tumors being enhanced by diminished HRR due to VEGFR3 inhibition. However, experimental *in vivo* efficacy data showed that the combination exhibited broad anti-tumor activity independent of HRR and that the combination effect was largely driven by influencing independent mechanisms affecting tumor cells and the tumor microenvironment (124). Clinically, the combination of cediranib and olaparib also showed some activity in the CONVERTO trial, a single-arm Phase IIb study of the two compounds in heavily pretreated, platinum-resistant, non-germline *BRCA*-mutated patients. However, the target objective response rate (ORR) of 20% was not reached (15.6%) and the overall benefit was unclear (OS 13.2 months, 95% CI 9.4–16.4; PFS 5.1 months, 95% CI 3.5–5.5) given it was a single arm study in a disease setting where most patients are expected to progress or die within 12 months (125). A Phase III trial [NCT02446600] in patients with relapsed platinum-sensitive ovarian cancer found that neither the combination of olaparib and cediranib nor olaparib monotherapy improved PFS compared to standard chemotherapy (126). An ongoing Phase II/III trial (NCT02502266) is evaluating cediranib plus olaparib compared to their monotherapies and standard chemotherapy. It remains to be determined if there is a clinical benefit of VEGF receptor inhibitors in treating EOC, particularly in chemoresistant HRP tumors. Future research efforts must focus on identifying other predictive biomarkers for anti-angiogenic therapy, as not all observed responses can be explained by *BRCA* mutation or HR-status.

Secondary cytoreductive surgery

There have been significant advances in the surgical management of HGSC with improved PFS and OS due to intensification of surgical efforts (62, 127, 128). A multicenter, open-label, randomized, controlled Phase III trial SOC-1 (NCT01611766) demonstrated in 357 patients with platinum-sensitive relapsed ovarian cancer that secondary cytoreductive surgery (SCS) followed by chemotherapy was associated with significantly longer PFS than with chemotherapy alone (median 17.4 vs 11.9 months, HR 0.58, 95% CI 0.45–0.74, $P<0.0001$) (129).

Furthermore, the DESKTOP III trial (NCT01166737) analyzed 407 patients with platinum-sensitive recurrent ovarian cancer and showed that SCS followed by chemotherapy leads to a longer OS than chemotherapy alone (median 53.7 vs 46.0 months, HR for death 0.75, 95% CI 0.59–0.96, $P=0.02$). Patients with a complete resection had the most favorable outcome (130). In addition to these two positive studies, in the GOG-0213 trial, which also included patients with platinum-sensitive, recurrent ovarian cancer, SCS followed by chemotherapy did not result in a longer OS than chemotherapy alone (131). There are some differences between the trials that may explain the inconsistent results, such as the additional use of bevacizumab in the DESKTOP III trial (NCT01166737) or the process of selecting patients and centers (130). Therefore, it is important that patients are appropriately counseled about the option of SCS.

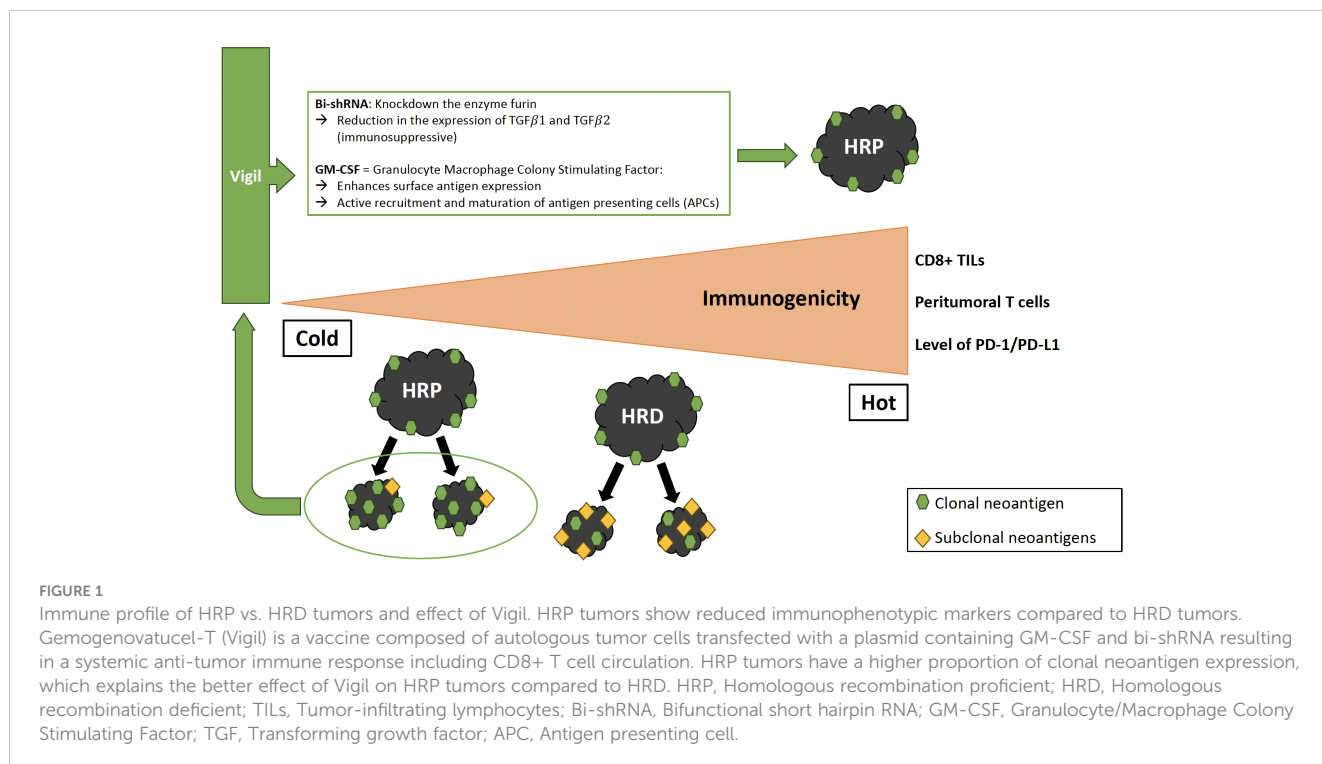
The role of surgery in patients with platinum-resistant disease has received increasing attention (132). In fact, patients with HRP tumors may benefit from SCS, similar to patients with low-grade serous ovarian cancer (133). To our knowledge, only three retrospective studies have been published analyzing the role of SCS in patients with platinum-resistant recurrent ovarian cancer. Both Petrillo et al. and Musella et al. showed a prolonged OS after recurrence when SCS was combined with chemotherapy instead of chemotherapy alone (median 32 months vs 8 months, $P=0.002$ and 67 months vs 24 months, $P=0.035$) (134, 135). However, when evaluating these two studies, it is important to consider that they were carried out before the PARPi era and therefore their conclusions must be put into perspective with current treatment options. A recent multicenter retrospective series by Tuninetti et al. in 50 heavily pretreated platinum-resistant ovarian cancer patients showed a statistically significant longer OS in the group of patients who received complete cytoreduction after SCS compared to the very low survival of patients with residual disease (median 33 months vs 5 months, HR 4.21, 95% CI 2.07–8.60, $P=0.001$) (136). These retrospective studies did not include stratification by *BRCA* mutation or HR-status, and any discussion of the extent of surgical clearance should also consider how residual disease may be a marker of biology that drives outcome. However, in a recent multicenter retrospective study investigating platinum sensitive recurrent ovarian cancer, SCS was shown to be effective in *BRCA*-wildtype patients, with an improvement in post-recurrence survival (PRS) when complete resection was performed (5-year PRS of 54% vs 42%, $P=0.048$), whereas in *BRCA*-mutated patients, prognosis appears to be related to molecular tumor characteristics rather than tumor resectability (137). A current prospective randomized controlled trial (NCT05633199) is now comparing SCS in platinum-resistant recurrent ovarian cancer and is expected to provide further information on whether and to what extent SCS can be used in the “platinum-resistant” HRP HGSC subgroup. Another advantage of SCS is to opportunistically obtain more comprehensive information on the pathological and molecular characteristics of HRP HGSC and how this may affect tumor evolution and clinical outcome (127). SCS in HGSC warrants further investigation in prospective trials, with particular attention paid to patient *BRCA* and HR-status.

Immunotherapy and antibody-drug conjugates

Immunotherapy for HGSC has fallen short of expectations, with immune checkpoint inhibitors so far showing limited benefit in ovarian cancer (138–142). However, there are new, potentially promising approaches, including ADCs that deliver a toxic ‘payload’ of chemotherapy directly to cancer cells via a linker attached to an antibody that binds to a specific surface antigen expressed on cancer cells (143). Mirvetuximab is a first-in-class ADC targeting folate receptor α (FR α), a cell surface protein that is commonly overexpressed on ovarian cancer (80–100%) and minimally expressed on normal tissue (144–146). This ADC incorporates the maytansinoid DM4 payload, a potent tubulin-targeting antimetabolic agent, and is the first novel agent to demonstrate an OS benefit when used as a single agent compared to chemotherapy alone in platinum-resistant ovarian cancer, as shown in the MIRASOL Phase III clinical trial (NCT04209855) (144). Patients with platinum-resistant, FR α -positive ovarian cancer treated with mirvetuximab (n=227) experienced an OS of 16.46 months (95% CI, 4.46–24.57) vs 12.75 months (95% CI, 10.91–14.36) for the chemotherapy arm (HR 0.67, 95% CI 0.50–0.89, $P=0.005$) and showed fewer Grade 3 or higher adverse events with mirvetuximab than with chemotherapy (41.7% vs 54.1%).

Another promising immunotherapy approach is Gemogenovatucl-T (Vigil, formerly known as FANG[®]), the first immunotherapy to demonstrate specific efficacy in the frontline maintenance setting for the HRP population. Vigil is a vaccine composed of autologous tumor cells derived from malignant tissue removed during cytoreductive surgery (147) (Figure 1). Tumor cells

are transfected with a plasmid containing GM-CSF and bi-shRNA to reduce furin activity, which subsequently downregulates the expression of the immunosuppressive proteins TGF- β 1 and TGF- β 2 (transforming growth factor β). This is important because the expression of furin and the resulting immunosuppressive TGF- β isoforms are increased in ovarian tumors compared to normal ovarian tissue (148). Long-term safety of Vigil and evidence of patient benefit have been demonstrated in multiple solid tumors, including advanced ovarian cancer (149, 150). The ongoing Phase IIB VITAL trial (NCT02346747) evaluated the efficacy of Vigil in patients with stage III/IV ovarian cancer. RFS was 11.5 months for patients treated with Vigil versus 8.4 months for patients treated with placebo (HR 0.69, 90% CI 0.44–1.07, $P=0.078$) with an acceptable toxicity profile (151). Although the primary endpoint of RFS was not met, a small subgroup analysis (n=45) showed that RFS and OS was significantly improved with Vigil compared to placebo in HRP patients (HR 0.38 and 0.34, 90% CI 0.2–0.75 and 0.14–0.83, $P=0.007$ and $P=0.019$), while no difference was seen in patients with BRCA-mutated disease (151, 152). Vigil increases the expression of cancer-associated neoantigens by upregulating MHC-II and processing by dendritic cells, which enhances the afferent immune response, the initial phase of immune activation characterized by antigen presentation and recognition, resulting in a systemic anti-tumor immune response including CD3+/CD8+ T cell circulation (152). T cells showed to preferentially recognize clonal neoantigens over subclonal neoantigens to target the tumor in lung adenocarcinoma and melanoma (153). HRP tumors are associated with higher clonal neoantigen expression compared to HRD tumors, which therefore contain higher proportions of subclonal neoantigen subpopulations, which may explain why



Vigil is more effective on HRP tumors (152). A Phase III trial is planned to validate the efficacy of Vigil compared to bevacizumab and niraparib in the HRP ovarian cancer population (152). It has been suggested that the increased expression of clonal tumor neoantigens and reduced tumor suppressive effect of TGF- β may synergistically enhance the activity of checkpoint inhibitor treatment (84, 154, 155). A prospective, randomized Phase I trial of Vigil plus the immune checkpoint inhibitor atezolizumab in patients with recurrent ovarian cancer explored this approach and showed that the combination was safe, supporting further investigation of this combination, particularly in *BRCA*-wildtype patients (155).

Adoptive cell therapy is another emerging personalized form of immunotherapy in which patients are treated with their *ex vivo* expanded natural TILs, genetically engineered T lymphocytes (CAR T cells) or T-cell receptor (TCR)-engineered T cells, which could offer a potential therapeutic option for patients with cold tumors. To date, CAR T cells that have been tested in clinical trials for HGSC have not yet demonstrated clear benefit (84, 156). While this technology is promising, further development is required to investigate the full potential of T cell engineering and other novel immunotherapy approaches to address the problem of immunologically cold tumors (84).

Combined targeted therapies

Rational drug combinations are a potential strategy to prevent or delay the development of resistance and offer the opportunity to improve the therapeutic window by potentially reducing the required drug doses, resulting in fewer side effects (70). Several strategies to selectively disrupt HRR in cancer cells with drugs have been investigated both preclinically and in clinical trials in HGSC or EOC in general, including HRP tumors, and have provided the rationale for new potential therapeutic approaches (Figure 2, Table 2). Here we review the most promising approaches for HRP tumors that have been or are being investigated in ovarian cancer, including targeting the CDK, P13K/AKT or CHK pathways.

CDK pathway

Approximately 40% of HGSC with HR-proficiency have an amplification of *CCNE1* (64). Cyclins are typically regulatory proteins that modulate the activity of CDKs (65). The CDK pathway offers attractive targets for the treatment of *CCNE1*-amplified tumors due to its role as the kinase partner of cyclin E1 in the activated cyclin E1/CDK complex (65, 163) (Figure 3). Cyclin E1 is primarily regulated by *CDK2* in *CCNE1*-amplified tumors, which are selectively dependent on *CDK2* activity (73). Combination therapy with the multi-CDK inhibitor dinaciclib (targets *CDK1/2/5/9*) has shown positive preclinical responses in *CCNE1*-amplified HGSC (164–166), and there is currently an active but not recruiting Phase I trial [NCT01434316] evaluating dinaciclib in combination with the PARPi veliparib in advanced solid tumors. However, a disadvantage of broad-spectrum CDK inhibitors is their high toxicity (167). Recently, more selective *CDK2* inhibitors have been investigated (74–76), including promising preclinical results using INX-315, a novel, potent and highly selective *CDK2* inhibitor. INX-315 treatment resulted in tumor growth inhibition of *CCNE1*-amplified tumors by promoting retinoblastoma protein hypophosphorylation, inducing cell cycle arrest and delaying the onset of *CDK4/6* inhibitor resistance in breast cancer (74). In addition, a recent first-in-human Phase I/IIa study (NCT04553133) of a novel and potent selective *CDK2i* (PF-07104091) found that it was well tolerated and showed antitumor activity in heavily pretreated metastatic breast cancer patients who had progressed on prior *CDK4/6* inhibitors (75). Further development of selective *CDK2* inhibitors in Phase I/II clinical trials are ongoing and may be of major importance for HRP HGSC.

Another strategy is to target Wee1-like kinase (WEE1), which is highly upregulated in HGSC (108). Its inhibition causes activation of *CDK1* and *CDK2*, resulting in cell cycle acceleration with an early mitotic entry and mitotic catastrophe leading to irreparable DNA damage (121). The multicenter Phase II IGNITE trial [ACTRN12619001185156P] is a non-comparative trial evaluating the WEE1-inhibitor adavosertib in two cohorts of platinum resistant recurrent HGSC (cyclin E1 overexpressed/*CCNE1*

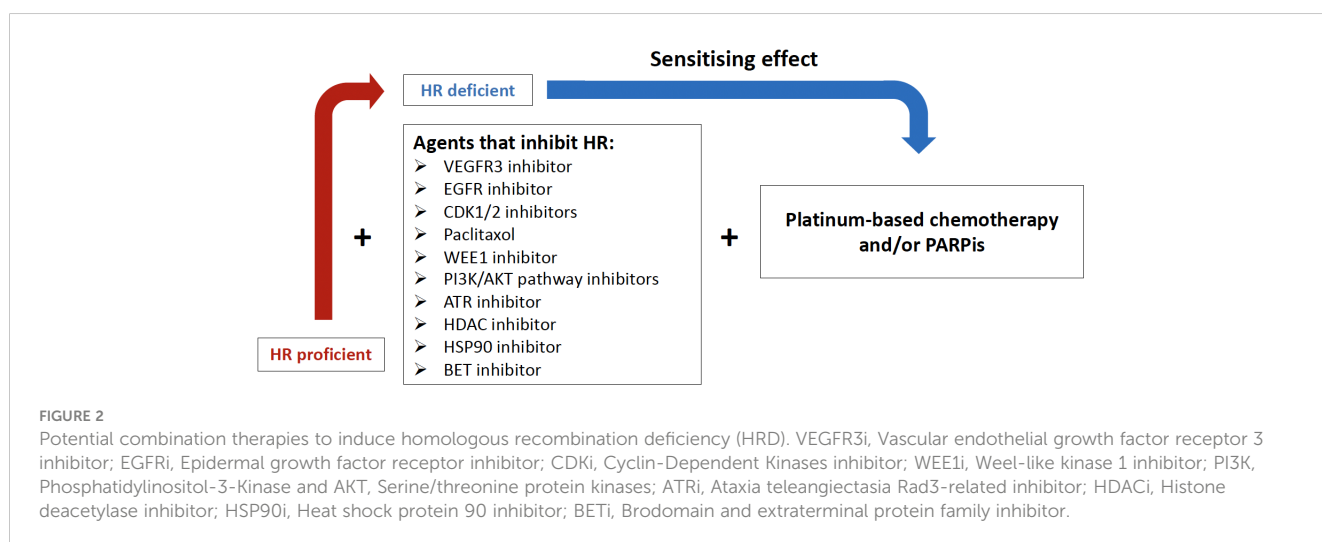


TABLE 2 Clinical trials of potential therapy options for HRP HGSC.

Combinations	Mode of action/possible mechanism of HR suppression	Drug	Phase	Status	Indication	No. of patients	Clinical notes & No. of HRP patients and their evaluation/ biomarkers	Study title and references	Clinical-trials.gov
Chemotherapy + PARPi	Veliparib may induce a chemo-sensitizing effect.	Carboplatin/ Paclitaxel + Veliparib	III	Completed	Newly diagnosed Stage III or IV, high-grade serous, epithelial ovarian, fallopian tube, or primary peritoneal cancer	1140	Improved PFS in HRP tumors (HR 0.76) 372 HRP tumor patients determined by myChoice® assay	VELIA: A Phase III Placebo-Controlled Study of Carboplatin/ Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib in Subjects With Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (27, 101, 112, 113)	NCT02470585
PARPi		Niraparib	III	Active, not recruiting	First-line maintenance therapy of advanced ovarian cancer Stage III or IV in complete or partial response to platinum-based chemotherapy	733	Significantly increased PFS (13.8 vs 8.2 months; HR 0.62, p < 0.001) regardless of the presence or absence of HRD, in HRP tumors 8.1 vs 5.4 months (HR 0.68) 249 HRP tumor patients determined by myChoice® assay	PRIMA: A Phase 3, Randomized, Double-Blind-Placebo-Controlled Multicenter Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy (20)	NCT02655016
PARPi + VEGFR3 inhibitor	Downregulation of <i>BRCA1/2</i> gene expression	Olaparib + Cediranib	II/III	Active, not recruiting	Recurrent platinum-resistant or refractory ovarian, fallopian tube or primary peritoneal cancer	562	Cediranib is a VEGFR1, VEGFR2 and VEGFR3 inhibitor Retrospective assessment of HRP tumor patients determined by BROCA HR assay	A Randomized Phase II/III Study of the Combination of Cediranib and Olaparib Compared to Cediranib or Olaparib Alone, or Standard of Care Chemotherapy in Women With Recurrent Platinum-Resistant or Refractory Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (COCOS)	NCT02502266
PARPi + EGFR inhibitor	Using synthetic lethality to increase DNA damage	Niraparib + Neratinib	I	Recruiting	Platinum resistant ovarian cancer and other advanced solid tumors	45		iNNOVATE: Phase I/Ib Clinical Trial of Niraparib and Neratinib in Advanced Solid Tumors With an Expansion Cohort in Platinum-resistant Ovarian Cancer	NCT04502602
Vaccine	Enhanced expression of clonal tumor neoantigen and reduced tumor	Gemogenovatucl-T (Vigil)	II	Active, not recruiting	Stage IIb, IIc or IV high-grade papillary serous/clear cell/endometrioid ovarian,	92	A companion clinical Phase II study investigated the combination of Atezolizumab and Vigil in Patients with	VITAL: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial of Vigil Engineered Autologous Tumor Cell	NCT02346747

(Continued)

TABLE 2 Continued

Combinations	Mode of action/possible mechanism of HR suppression	Drug	Phase	Status	Indication	No. of patients	Clinical notes & No. of HRP patients and their evaluation/ biomarkers	Study title and references	Clinical-trials.gov
	suppressor activity of TGF- β				fallopian tube or primary peritoneal cancer		advanced gynecological cancers (155) 45 HRP tumor patients, retrospective analyzed determined by myChoice [®] assay	immunotherapy in Subjects With Stage IIIb-IV Ovarian Cancer in Clinical Complete Response Following Surgery and Primary Chemotherapy (151)	
PARPi + immune checkpoint inhibition (+/- bevacizumab)	Synergistic activity by PARPis activating immune responses	Rucaparib + Nivolumab	III	Active, not recruiting	Advanced high-grade epithelial ovarian, primary peritoneal or fallopian tube cancer who achieved response after cytoreductive surgery and initial platinum-based chemotherapy	1000	Primary outcome is PFS. Primary results of ATHENA-MONO (rucaparib monotherapy) demonstrated improved PFS also in HR proficient patients (12.1 vs 9.1 months; HR 0.65) (13). 44.2% HRP tumor patients, determined by FoundationOne CDx	ATHENA: A multicenter, randomized, double-blind, placebo-controlled Phase III Study in ovarian cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy (25)	NCT03522246
		Olaparib + Durvalumab	I/II	Active, not recruiting	Patients with advanced solid tumors	264	Preliminary results of the combination in addition with bevacizumab showed an ORR of 75% in HRP patients (157) HRD status determined by FoundationOne CDx	A Phase I/II Study of MEDI4736 (Anti-PD-L1 antibody) in Combination With Olaparib (PARP inhibitor) in Patients With Advanced Solid Tumors	NCT02734004
		Durvalumab + Chemotherapy + Bevacizumab + Olaparib	III	Active, not recruiting	Newly diagnosed advanced ovarian cancer	1407	The HRP subgroup had a consistent PFS effect (HR 0.68, 95%, 0.34–0.86), safety was generally consistent (158) 55% HRP tumor patients determined by myChoice [®] assay	A Phase III, Double-Blind, Placebo-Controlled, Multicenter Study of Durvalumab in Combination With Chemotherapy and Bevacizumab, Followed by Maintenance Durvalumab, Bevacizumab and Olaparib in Newly Diagnosed Advanced ovarian cancer patients (DUO-O)	NCT03737643
Selective CDK2 inhibitor	Rb hypophosphorylation and reduction of CDK2 results in durable control of	INX-315	I/II	Recruiting	Advanced cancer, including ovarian cancer with <i>CCNE1</i> -ampl.	81	INX-315 is a selective inhibitor of CDK2 Biomarker for HRP tumor patients: <i>CCNE1</i> -amplification	A Phase I/II, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of INX-315	NCT05735080

(Continued)

TABLE 2 Continued

Combinations	Mode of action/possible mechanism of HR suppression	Drug	Phase	Status	Indication	No. of patients	Clinical notes & No. of HRP patients and their evaluation/ biomarkers	Study title and references	Clinical-trials.gov
	tumor growth in <i>CCNE1</i> -amplified tumors	BLU-222	I/II	Recruiting	Advanced cancer, including ovarian cancer with <i>CCNE1</i> -amplification	366	BLU-222 is a selective inhibitor of CDK2 Biomarker for HRP tumor patients: <i>CCNE1</i> -amplification	A Phase I/II Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of BLU-222 as a Single Agent and in Combination for Patients With Advanced Solid Tumors	NCT0525416
		PF-07104091	I/II	Recruiting	Advanced or metastatic small cell lung, breast and ovarian cancer	320	PF-07104091 is a selective inhibitor of CDK2, already tested successfully clinically in metastatic breast cancer (75)	Phase I/IIa Dose Escalation and Expansion Study of PF-07104091 As a Single Agent And in Combination Therapy	NCT04553133
PARPi + CDK inhibitor	Inhibition of phosphorylation of <i>BRCA1</i>	Veliparib + Dinaciclib	I	Active, not recruiting	Histologically confirmed diagnosis of a solid tumor for which no curative therapy exists	118	Dinaciclib is a multi-CDK inhibitor targeting CDK 1/2/5/9/12	Phase I Trial of ABT-888 and SCH727965 in Patients With Advanced Solid Tumors (159)	NCT01434316
PARPi + WEE1 inhibitor	Activation of <i>CDK1</i> resulting in cell cycle acceleration and mitotic catastrophe, leading to DNA damage	Olaparib + Adovertib	II	Recruiting	Ovarian cancer progressed during PARPi therapy	104	Combination shows greater CBR, but the ORR is similar. Better ORR in BRCA wildtype vs BRCA-mutated (39% vs 19%)	EFFORT: Efficacy of AZD1775 in PARP Resistance; a Randomized 2-Arm, Non-Comparative Phase II Study of AZD1775 Alone or AZD1775 and Olaparib in Women With Ovarian Cancer Who Have Progressed During PARP Inhibition (160)	NCT03579316
PKMYT1 inhibitor + ATR inhibitor	Downregulation of Myt1 kinase, whose primary role is the negative regulation of <i>CDK1</i> in <i>CCNE1</i> amplified cells	RP-6306 as monotherapy or with RP-3500	I	Recruiting	Locally advanced or metastatic resistant or refractory solid tumors with next generation sequencing report obtained demonstrating eligible tumor biomarker	180		Phase I of the Safety, Pharmacokinetics, Pharmacodynamics and Preliminary Clinical Activity of RP-6306 Alone or in Combination With RP-3500 in Patients With Advanced Solid Tumors	NCT04855656
Chemotherapy + PKMYT1 inhibitor		Gemcitabine + RP-6306	I	Active, not recruiting	Advanced solid tumors	104	Gemcitabine treatment enhances cyclin E-driven DNA replication stress leading to sensitization of cells and tumors to RP-6306	Phase I Study of the PKMYT1 inhibitor RP-6306 in Combination With Gemcitabine for the Treatment of Advanced Solid Tumors (MAGNETIC Study)	NCT05147272

(Continued)

TABLE 2 Continued

Combinations	Mode of action/possible mechanism of HR suppression	Drug	Phase	Status	Indication	No. of patients	Clinical notes & No. of HRP patients and their evaluation/ biomarkers	Study title and references	Clinical-trials.gov
PARPi + PI3K/AKT pathway inhibitors	ERK activation/ phosphorylation, increased activation of ETS1, and suppression of <i>BRCA1/2</i> expression	Olaparib + Alpelisib	II	Active, not recruiting	HGSC with no germline <i>BRCA</i> mutation detected	358	Alpelisib and Olaparib versus chemotherapy of physician's choice	EPIK-O: A Phase III, Multi-center, Randomized (1:1), Open-label, Active-controlled, Study to Assess the Efficacy and Safety of Alpelisib (BYL719) in Combination With Olaparib as Compared to Single Agent Cytotoxic Chemotherapy, in Participants With no Germline <i>BRCA</i> Mutation Detected, Platinum-resistant or Refractory, High-grade Serous Ovarian Cancer (161)	NCT04729387
		Olaparib + Capivasertib	IB/II	Active, not recruiting	Recurrent endometrial, triple-negative breast, and ovarian cancer	159		A Phase Ib Study of the Oral PARP Inhibitor Olaparib With the Oral mTORC1/2 Inhibitor AZD2014 or the Oral AKT Inhibitor AZD5363 for Recurrent Endometrial, Triple Negative Breast, and Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	NCT02208375
PARPi + ATR inhibitor	Restriction of the <i>CHK1</i> pathway and proteins of the <i>HRR</i> pathway	Olaparib + Ceralasertib	II	Recruiting	Recurrent EOC	86		Combination ATR and PARP Inhibitor (CAPRI) trial With AZD 6738 and Olaparib in Recurrent Ovarian Cancer	NCT03462342
PARPi + HDAC inhibitor	Downregulation of HR pathway genes	Talazoparib + Belinostat	I	Recruiting	Metastatic breast cancer, metastatic castration resistant prostate cancer, and metastatic ovarian cancer	25		A Phase I Dose-Escalation Trial of Talazoparib in Combination With Belinostat for Metastatic Breast Cancer, Castration Resistant Prostate Cancer and Ovarian Cancer	NCT04703920
PARPi + HSP90 inhibitor	<i>BRCA1</i> and other essential HR pathway genes are HSP90 client proteins	Olaparib + HSP90 inhibitor (AT13387)	I	Completed	Solid tumors that are metastatic or cannot be removed by surgery or recurrent ovarian, fallopian tube, primary peritoneal, or triple-negative breast cancer	28	No unexpected toxicities, prolonged disease stabilization, but no further development of the combination planned	A Phase I Study of PARP Inhibitor Olaparib and HSP90 Inhibitor AT13387 for Treatment of Advanced Solid Tumors With Expansion in Patients With Recurrent Epithelial Ovarian, Fallopian Tube, Peritoneal Cancer	NCT02898207

(Continued)

TABLE 2 Continued

Combinations	Mode of action/possible mechanism of HR suppression	Drug	Phase	Status	Indication	No. of patients	Clinical notes & No. of HRP patients and their evaluation/ biomarkers	Study title and references	Clinical-trials.gov
PARPi + BET inhibitor	Induction of DNA damage resulting in HRD phenotype	Talazoparib + ZEN003694	II	Recruiting	Recurrent ovarian, fallopian tube or primary peritoneal cancer	33		or Recurrent Triple-Negative Breast Cancer (162) Phase II Study of a BET Inhibitor, ZEN003694, Combined With a PARP Inhibitor, Talazoparib, in Patients With Recurrent Ovarian Cancer	NCT05071937

PARPi, Poly ADP-ribose polymerase inhibitors; N, Number of patients; HR, Hazard ratio; HRP, Homologous recombination proficiency; PFS, Progression-free survival; OS, Overall survival; RB, Retinoblastoma protein; EOC, Epithelial ovarian cancer; ORR, Objective response rate; CBR, Clinical benefit rate.

amplified and cyclin E1 overexpressed/*CCNE1* non-amplified) and demonstrated an ORR of 53% and a clinical benefit of 61% in an interim analysis of 32 patients in the cyclin E1 overexpressed/*CCNE1* non-amplified cohort (168). *CDK1* is a key cell-cycle regulator and phosphorylates *BRCA1*, which is required for DNA damage-induced checkpoint control through the formation of *BRCA1*-containing foci (169); consequently, inhibition of *CDK1* impairs the ability of cells to functionally repair DNA by HRR (165). Therefore, depletion or inhibition of *CDK1* creates a state of “BRCAness” in transformed cells (170). Results from preclinical studies in other cancer modalities support the effect of *WEE1* inhibition on HR, and thus the assumption that *WEE1* inhibitors, in combination with a DNA damaging agent, specifically render HRP cell lines more susceptible to treatment (171, 172).

An ongoing Phase II trial (NCT03579316) in recurrent PARPi-resistant EOC (including 98% HGSC) is evaluating the efficacy of the *WEE1* inhibitor adavosertib with or without olaparib. The combination showed to have a greater clinical benefit rate than adavosertib alone (89% vs 63%), but the ORR was similar between the two arms (160). Interestingly, exploratory analyses showed a larger benefit of the combination in the *BRCA*-wildtype subgroup compared to the *BRCA*-mutated subgroup (39% vs 19% ORR). Translational analyses are underway to further explore potential predictive biomarkers (160). However, adavosertib use requires consideration of single agent toxicity as well as interactions when used as a drug combination. For example, the use of adavosertib in combination with carboplatin showed an increased incidence of bone marrow suppression, diarrhea, vomiting and fatigue (168, 173). Additionally, adavosertib is metabolized via the enzyme cytochrome P450 3A4 (*CYP3A4*), which means that patients receiving any co-medications that are strong *CYP3A4* inhibitors (for example, antibacterials such as clarithromycin and erythromycin, anticancer agents such as tamoxifen and irinotecan, anti-HIV agents such as ritonavir and delavirdine, or antihypertensives such as dihydro-dralazine and verapamil) (174) would be excluded from clinical trials.

Another promising therapeutic target of the *CDK* pathway specifically for *CCNE1*-amplified HGSC is *PKMYT1* (68). *PKMYT1* is a kinase encoding the pro-protein kinase Myt1, a negative regulator of *CDK1*, and was identified in a genetic screen of cellular dependencies in *CCNE1* amplified HGSC (68). Inhibition of *PKMYT1* results in activation of *CDK1*, causing unscheduled mitotic entry and genome instability. In contrast, the *WEE1*inhibitor showed no selectivity towards *CCNE1*-amplified cell lines (175, 176). Ongoing first-in-human clinical trials are evaluating the *PKMYT1* inhibitor lunresertib (RP-6306) as monotherapy or in combination with the ataxia-telangiectasia Rad3-related (*ATR*) inhibitor RP-3500 (NCT04855656) and in combination with gemcitabine (NCT05147272) in advanced solid tumors.

PI3K/AKT pathway

Phosphatidylinositol 3-kinase (*PI3K*) activity is stimulated by a wide range of oncogenes and growth factor receptors (177) and the

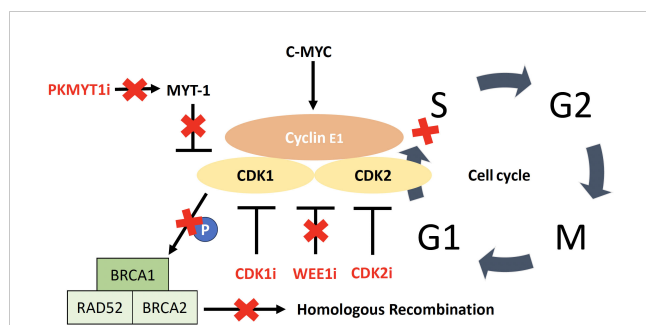


FIGURE 3

CDK/cyclin E1 complex including targets for therapy. Activation of CDK2 by cyclin E1, allowing the cell to enter the S phase. Overexpression of cyclin E1 increases the rate at which cancer cells transition from G1 to S phase, leading to replicative stress and genomic instability. The WEE1 kinase is involved in regulating cell cycle progression by inhibiting CDK1 and CDK2 and WEE1 inhibition leads to cell cycle acceleration, with early mitotic entry and consequent mitotic catastrophe leading to irreparable DNA damage. CDK1 phosphorylates BRCA1 and CDK1 inhibition impairs the ability of cells to carry out functional DNA repair through homologous recombination. PKMYT1 encodes the protein kinase Myt1, a negative regulator of CDK1.

activity of the PI3K pathway is important to the development of drug resistance in a variety of cancer types and treatment settings (178). Inhibition of the PI3K pathway also results in PI3K-mediated downregulation of *BRCA*, accompanied by extracellular signal-regulated kinase (ERK) phosphorylation and subsequent abrogation of HRR (179). Preclinical work in ovarian cancer patient-derived xenograft models has shown that the PI3K inhibitor alpelisib (BYL719) inhibits HRR and consequently sensitizes ovarian cancer models with *de novo* or acquired HR-proficiency to olaparib (180). A Phase I study in 28 patients with EOC (75% HGSC) provided preliminary clinical evidence of the efficacy of the combination of olaparib and alpelisib. An ORR of 33% was seen in patients with *BRCA*-wildtype platinum-resistant EOC compared to an ORR of 3–10% with olaparib or other PARPi monotherapy in the same setting, and with acceptable toxicity (121, 181). Importantly, objective responses to this combination of agents occurred regardless of HR status, as measured by targeted DNA sequencing (181). Further evidence will be provided by the ongoing Phase III EPIK-O/ENGOT-OV61 trial (NCT04729387), which is evaluating the efficacy and safety of alpelisib/olaparib compared to single-agent cytotoxic chemotherapy in patients with platinum-resistant or refractory *BRCA*-wildtype HGSC (161).

The AKT serine/threonine protein kinases (*AKT1*, *AKT2*, *AKT3*) are key downstream mediators of PI3K signaling (182, 183) and in particular, *AKT2* has emerged as a poor prognostic marker and potential target in EOC (34, 70, 71). Drugs targeting AKT have shown activity in breast, endometrial, and ovarian cancer and are currently being investigated in Phase I/II/III trials (183, 184). An active Phase Ib/II trial (NCT02208375) is evaluating the combination of olaparib and the AKT inhibitor capivasertib (AZD5363) in a heavily pretreated cohort of 159 patients, with encouraging clinical activity regardless of the presence of a *BRCA* mutation and despite platinum resistance (183). Further studies are needed to explore the potential of AKT and PI3K inhibitors in

combination with PARPi or as monotherapy in HRP HGSC and ovarian cancer in general.

ATR inhibitors

ATR has a major role in the CHK1 (checkpoint kinase 1) pathway of DNA repair and is a regulator of several proteins in the HRR pathway, including activation of *BRCA1*, *PALB2* and *RAD51* (108). The potential for mechanistic synergism between ATR inhibitors (ATRi) and PARPis has been demonstrated in HRD and HRP ovarian cancer cells in preclinical models (108, 185, 186). Acquisition of PARPi resistance was shown to be associated with increased ATR-CHK1 activity, further supporting the potential benefit of combining of PARPis with ATR inhibitors (185). Patient-derived xenograft models of *BRCA*-wildtype and *CCNE1*-amplified platinum-resistant ovarian cancer, which are associated with increased baseline activation of ATR/CHK1, demonstrated tumor reduction and a significant increase in OS when treated with the combination of PARPi and ATRi (185). Based on these preclinical data, an ongoing Phase II clinical trial of ceralasertib (AZD6738) in combination with olaparib was developed and initial results demonstrated the potential of ATRi to overcome PARPi resistance in an HRD HGSC patient population (187).

ATRis are also being investigated as potential monotherapy, and preliminary anti-tumor activity has been demonstrated in heavily pretreated tumors across a range of histologic types and gene alterations (188). Initial results from TRESR, a phase I trial of ATRi monotherapy with camonsertib, support preclinical findings that ATRi may be clinically active in other patient populations beyond those with loss of function of ataxia telangiectasia mutated (*ATM*) kinase, including those with other gene alterations (e.g., *ARID1A*, *CCNE1*, and *MYC*) or phenotypic (replication) markers (188, 189). The functional assessment of replication stress biomarkers is thought to be a better predictive biomarker for ATRi response than single aberrant genes in ovarian cancer (190). This statement can also be applied to the selective CHK1/2 inhibitor prexasertib, which showed an increased sensitivity to platinum and olaparib in mouse tumor transplantation models and monotherapy efficacy in *BRCA*-wildtype platinum-resistant ovarian cancer (191, 192). To date, however, there is limited data on the safety and anti-tumor activity of CHK inhibitors, and a phase II trial of prexasertib was recently terminated prematurely due to COVID-19 and a shortage of investigational drug supplies (193).

HDAC inhibitors

The altered expression of HDACs (histone deacetylases) has been associated with resistance to platinum-based chemotherapy and poor prognosis (194) and HDAC inhibition leads to impaired HRR in cancer cells through reduced expression of critical genes such as *BRCA1* and *RAD51* (195, 196). Konstantinopoulos et al. provided a preclinical rationale for the use of HDAC inhibitors (HDACi) to reduce HRR in HRP ovarian cancer, including *CCNE1*-amplified tumors, as a means to enhance PARPi activity (197). This approach

has been confirmed by further preclinical studies showing that HDACi such as suberoylanilide hydroamic acid (SAHA), romidepsin, panobinostat and entinostat are synergistic with PARPi in HRP ovarian cancer cells (197, 198). HDACi downregulate genes in the cyclin E/CDK and HR signaling pathways and thus show a synergistic cytotoxic effect in combination with a PARPi (198–200). Based on these preclinical results, there is an ongoing Phase I dose-escalation trial (NCT04703920) of the combination of the PARPi talazoparib and the HDACi belinostat in metastatic ovarian, breast and prostate cancer.

HSP90

Another attempt to extend the benefit of PARPis to HRP patients is their combination with the heat shock protein 90 (HSP90) inhibitors. HSP90 mediates the maturation, stability and activation of several key proteins involved in DNA repair and HRR, such as CDK1, BRCA1 and BRCA2 (201). Due to its abundant expression, its dependence on adenosine ATP (adenosine triphosphate), and its massive protein interactome, it is an ideal target for pharmacological inhibition (201). Inhibition of HSP90 by ganetespib (STA-9090), a second-generation HSP90 inhibitor, sensitized HRP HGSC cells to talazoparib (201). HSP90 inhibition resulted in downregulation of *BRCA1* and *RAD51*, HRR impairment and increased DNA damage (202). A recent Phase I dose-escalation study showed that the combination of the HSP90i onalespib and olaparib resulted in prolonged disease stabilization, without dose limiting toxicities, in a heavily pretreated patient population with advanced solid tumors (162). Due to limited efficacy as a monotherapy and in other combination studies, further development of onalespib was discontinued (162). However, preclinical and clinical data may support future evaluation of novel combinations of PARPis with other HSP90 inhibitors, such as pimitespib (203). While HSP90 inhibition has the potential to sensitize HRP HGSC to PARPi and other DNA-damaging agents, further clinical research is needed.

BET inhibitors

The BET (bromodomain and extraterminal) protein family includes BRD4, an epigenetic transcription modulator involved in the expression of proteins that regulate the cell cycle and DNA repair (204). BRD4 has been shown to be a necessary factor for the proliferation and survival of HGSC cells (205). In addition, *BRD4* amplification is mutually exclusive with *BRCA1* and *BRCA2* mutations and tends to co-occur with *CCNE1* amplification in HGSC, so BET inhibition may be particularly promising in the HRP group (38, 206–208). Preclinical studies have shown that BET inhibitors (BETis) suppress the expression of *WEE1* and *TOPBP1* (DNA Topoisomerase II Binding Protein 1) (209, 210). *WEE1* and *TOPBP1* play critical roles in cellular processes related to DNA damage response and cell cycle regulation. *WEE1* is a protein kinase that regulates the G2/M checkpoint in the cell cycle, controlling entry into mitosis and allowing time for DNA repair (173, 176, 211,

212). *TOPBP1* acts as a scaffold protein that coordinates the activation of ATR kinase in response to DNA damage, thereby initiating signaling cascades essential for DNA repair and cell cycle arrest (213). Dysfunction or dysregulation of these proteins can lead to genomic instability and contribute to the development of diseases such as cancer. Additionally, increased BRD4 expression has been identified as a factor contributing to PARPi resistance in HGSC (210). The specific BRD4 inhibitor INCB054329 was able to directly decrease the activity of both *BRCA1* and *RAD51* and induce an HRD phenotype (108, 209). Consequently, in combination with PARPis, a synergistic effect is observed with decreased HR activity, increased DNA damage, and consequently increased tumor cytotoxicity (108, 214). Unfortunately, initial clinical studies involving single agent use of BET inhibitors in various tumor types were disappointing, as preclinical results could not be replicated and resistance to therapy occurred rapidly in some cases (215). Specific evidence in ovarian cancer will be provided by an ongoing Phase II clinical trial (NCT05071937) of the BETi ZEN003694 in combination with the PARPi talazoparib in patients with recurrent ovarian cancer who have progressed on prior PARPi therapy.

Summary

The HRP HGSC subgroup exhibits complex molecular heterogeneity combined with an immune depleted microenvironment, and these are associated with therapy resistance and a poor prognosis. A subset of these cancers are driven by *CCNE1* amplification and PI3K/AKT alterations that contribute to cell cycle dysregulation and thus these pathways represent promising targets for novel therapeutic approaches. However, a significant subset of HRP HGSC lack *CCNE1* amplification, and the molecular drivers of these cancers are still being defined. Additional studies, including the use of cell lines and potentially the use of existing data from systematic knockdown and knockout genetic screens (216, 217) in the HRP non-*CCNE1* amplified subgroup may define critical dependencies.

A large proportion of HRP HGSC are relatively immune depleted, likely in part due to a reduced mutational burden associated with intact DNA repair. The development of novel immunotherapies to boost the anti-tumor immune response remains a key area of focus for HRP tumors, including personalized approaches to enhance T-cell infiltration with therapeutic vaccines or adoptive cell therapy. Several new combination treatments are under investigation, which aim to sensitize HRP cancers to existing therapies, such as platinum and PARPis, by targeting the HRR pathway and impairing the ability of cells to functionally repair DNA. Antibody drug conjugates also represent a promising class of therapies to increase the potency and specificity of highly potent cytotoxic agents, while reducing toxicity.

These new approaches offer the opportunity to expand the otherwise very limited treatment options for patients with HRP HGSC. Importantly, explicit identification and enrollment of patients with HGSC tumors known to have intact HRR in clinical trials is crucial for the development of effective therapies for this medically underserved group.

Author contributions

NS: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. DG: Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition. GA-Y: Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology. DB: Writing – review & editing, Supervision, Resources, Project administration, Methodology. VH-S: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Conceptualization. TZ: Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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