

Further Understanding of High-Grade Serous Ovarian Carcinogenesis: Potential Therapeutic Targets

This article was published in the following Dove Press journal:
Cancer Management and Research

Ioannis A Voutsadakis ^{1,2}

¹Algoma District Cancer Program, Sault Area Hospital, Sault Ste. Marie, Ontario, Canada; ²Section of Internal Medicine, Division of Clinical Sciences, Northern Ontario School of Medicine, Sudbury, Ontario, Canada

Abstract: High-grade serous ovarian carcinoma (HGSOC) is the most common type of ovarian cancer and the most lethal gynecologic malignancy due to advanced stage at presentation. Recent years have witnessed progress in the therapy of HGSOC with the introduction of PARP (poly-adenosine diphosphate ribose polymerase) inhibitors and the anti-angiogenic monoclonal antibody bevacizumab to the backbone of chemotherapy or as maintenance therapy after chemotherapy. The improved molecular understanding of ovarian cancer pathogenesis, which has brought these therapies into the clinic, aspires to extend the boundaries of therapies through elucidation of other molecular aspects of ovarian carcinogenesis. This accumulating knowledge has started to be translated to additional targeted therapies that are in various stages of development. These include inhibitors of the function of other proteins involved in homologous recombination deficiency (HRD), such as WEE1 kinase, ATM/ATR kinases and CDK12 inhibitors. Despite disappointing results with immune checkpoint inhibitors monotherapy, harnessing the immune system in HGSOC with combination therapies that promote antigen production and immune cell activation is an avenue being explored. This paper examines arising HGSOC therapies based on molecular understanding of pathogenesis.

Keywords: ovarian cancer, serous, genomics, targeted therapies, adavosertib, immunotherapy

Introduction

Although it is only third in prevalence among gynecologic cancers, behind cervical and endometrial cancer, ovarian cancer is a highly lethal disease. High-grade serous ovarian carcinomas (HGSOC) represent the majority of ovarian cancers and are responsible for even a higher percentage of the mortality from ovarian cancer.¹ Over the last several years, sub-types of epithelial ovarian cancers with different morphopathological and molecular characteristics have been elucidated. At least five subtypes are currently categorized as distinct entities. Those include, besides HGSOC, clear cell carcinomas and endometrioid carcinomas characterized by *ARID1a*, *PIK3CA* and *PTEN* mutations and low-grade serous ovarian carcinomas (LGSOC) and mucinous carcinomas that are characterized by *KRAS* mutations.^{2,3} In addition, LGSOC present commonly *BRAF* mutations and some mucinous carcinomas have molecular abnormalities in *ERBB2* gene encoding for HER2 protein.⁴

HGSOC are characterized overall by a low total number of mutations. The only commonly mutated gene is *TP53* which is mutated in 96% of cases in The Cancer

Correspondence: Ioannis A Voutsadakis
Algoma District Cancer Program,
Sault Area Hospital, 750 Great Northern
Road, Sault Ste Marie, ON P6B 0A8,
Canada
Email ivoutsadakis@yahoo.com

Genome Atlas (TCGA).⁵ No other tumor suppressors or oncogenes are mutated in more than 5% of cases. Notably, mutations in commonly mutated oncogenes such as *KRAS*, *BRAF*, *NRAS* and *PIK3CA* mutations are very rare in HGSOC (all less than 1% in TCGA). Thus, targeted therapies against commonly mutated, gain-of-function oncogenes are not possible in this disease. In contrast, HGSOC possess widespread copy number alterations (CNAs) that lead to an extremely complex genomic landscape.⁶ This landscape stems from a defective homologous recombination DNA repair machinery in more than half of HGSOC.⁶ Underlying defects include genomic or somatic mutations of *BRCA1* and *BRCA2* genes or other genes involved in homologous recombination.⁷ As a result, therapeutic opportunities may arise in HGSOC from targeting vulnerabilities stemming from the defective repair machinery, which have already been exploited with the clinical development and introduction of PARP (polyadenosine diphosphate ribose polymerase) inhibitors. Alternatively, recurrent amplifications of oncogenes that lead to increased expression and activity of their product proteins could provide targetable opportunities. In addition, despite the low tumor point mutation burden, the complex genomic landscape of HGSOC may be a source of neoantigens that can become exploitable for immunotherapies.

The current paper will discuss recent insights of the genetic constitution of HGSOC as they relate to the conception, design and development of new targeted therapies at the footsteps of PARP inhibitors.

The Landscape of HGSOC: Common and Uncommon Mutations and CNAs

HGSOC is characterized by a low tumor mutation burden (TMB) with a median of 69 mutations (interquartile range 48 to 103) in TCGA ovarian carcinoma study.⁵ Besides the almost universal mutations of *TP53*, few genes are mutated in a recurrent manner. *BRCA1* and *BRCA2* are somatically or genetically mutated in 22% of cases.⁴ Additionally, statistically significant, compared with the expected distribution models, but low number of mutations are observed in tumor suppressors *RBI* and *NF1* and in kinase *CDK12*.⁵ A signature of homologous recombination deficiency (HRD) is observed in about half of HGSOC. Some of the cases with HRD have no *BRCA1* or *BRCA2* mutations but possess defects in other repair genes or epigenetic defects

such as *BRCA1* promoter methylation.^{5,8} More rare germline mutations in other repair genes such as *BRIPI* (FANCI), *CHEK2*, *CHEK1*, *RAD51C* and deletions of *PTEN* have been observed in HGSOC.⁸ Promoter methylation of *RAD51C* has also been observed. The phenotype of HRD shared by *BRCA*-mutated and *BRCA*-unmutated cancers with repair defects has been termed “BRCAness”.⁹ Double strand DNA repair defects resulting from homologous recombination deficiency are associated with a widespread disarray in the HGSOC genome characterized by extensive copy number alterations, several of which are recurrent. TCGA identified 63 areas of recurrent focal amplifications and 50 areas of recurrent focal deletions. Most frequently amplified genomic loci, observed in more than 20% of cases, include oncogenes *CCNE1*, *MYC* and *MECOM* encoding for cyclin E, C-Myc and EVI1 proteins and located at chromosomes 12q12, 8q24 and 3q26, respectively. *CCNE1* gains or amplifications are mutually exclusive with *BRCA* mutations.⁸

The landscape of acquired chemotherapy-resistant ovarian cancers includes reversions of *BRCA* mutations that restore the function of the proteins and reverse the HRD.^{8,10} Moreover, loss of *BRCA1* promoter methylation and fusions involving the promoter of the gene *ABCB1* encoding the efflux pump MDR1 and leading to increased expression of the protein are recurrently observed.⁸ Other noticeable genomic changes during resistance development include increase in overall tumor mutation burden and occasional acquisition of structural variants in apoptosis promoting genes such as *FOXO1* and *BCL2L1* encoding for BCL2 family member BIM.

A study that examined mRNA expression of 23 genes of the extended PI3K-AKT network in HGSOC and clear cell carcinomas was able to separate the two sub-types and further identified two sub-sets of HGSOC with different prognoses.¹¹ The sub-set with better prognosis had higher expression of caspase 3, *XIAP* (X-linked Inhibitor of Apoptosis), *NFKB1*, *FAS* and *GSK3B* mRNAs. In contrast, the sub-set with the worse prognosis had a higher expression of mRNA for *CDH1*, encoding for E cadherin. Consistent with the mRNA expressions, HGSOC with co-expression of caspase 3 and *XIAP* proteins by immunohistochemistry had a better disease-free survival than counterparts without co-expression of the two proteins. Interestingly, caspase 3 was exclusively expressed in tumor macrophages and *XIAP* in tumor cells.¹¹

Building on PARP Inhibition

Earlier attempts for targeted treatments in ovarian cancers focused on hormone therapies given that female reproductive organs are targets of hormone action, and, in addition, focused on anti-angiogenic therapies such as the monoclonal anti-VEGF antibody bevacizumab and the VEGFR small tyrosine kinase inhibitor cediranib.^{12–14} PARP inhibitors were the first targeted therapy introduced in HGSOC in the modern era following the recognition of synthetic lethality with *BRCA1* and *BRCA2* mutations and later with other lesions producing HRD (Figure 1).¹⁵ BRCA-related HGSOC tend to present distinct histologic patterns termed SET (Solid areas, pseudo-Endometrioid and Transitional cell like) and, additionally, higher mitotic activity, necrosis and tumor-infiltrating lymphocytes (TILs).¹⁶ Several PARP inhibitors, including olaparib, niraparib and rucaparib, have been approved for the treatment of recurrent ovarian cancer after response to chemotherapy or, for olaparib and rucaparib, for germline BRCA-mutated ovarian cancers after chemotherapy progression (Table 1).^{17,18} Niraparib is also indicated in maintenance therapy after response to first-line chemotherapy and olaparib has an indication in combination with bevacizumab as maintenance therapy in patients with BRCA mutations or HRD positive tumors after chemotherapy. Two other PARP

inhibitors, talazoparib, which has been approved for breast cancer patients with BRCA mutations, and veliparib, have not yet gained regulatory approval in ovarian cancer.¹⁹ Although they have many common class characteristics, PARP inhibitors have also important differences. Veliparib, for example, possesses a weaker ability to trap PARP enzyme on DNA than other PARP inhibitors and is the only PARP inhibitor that may be given in combination with chemotherapy.^{20,21} However, most benefit is observed in disease that retain platinum chemotherapy sensitivity, while the effectiveness of PARP inhibitors in platinum refractory or resistant disease, where the greatest need for novel therapies exist, is lower.²² Thus, it is evident that mechanisms leading to platinum resistance under therapy pressure are overlapping with mechanisms that produce PARP inhibitor resistance.

To circumvent resistance, PARP inhibitors combinations with other therapies are currently explored based on the principles of either additive efficacy with other effective drugs in ovarian cancer (anti-angiogenics, chemotherapy) or on molecular rational (immune checkpoint inhibitors, cell cycle kinase inhibitors).²³ A combination that is intensely studied couples PARP inhibitors with immune checkpoint inhibitors. A preclinical rational for this combination has been provided by studies in mice that showed that

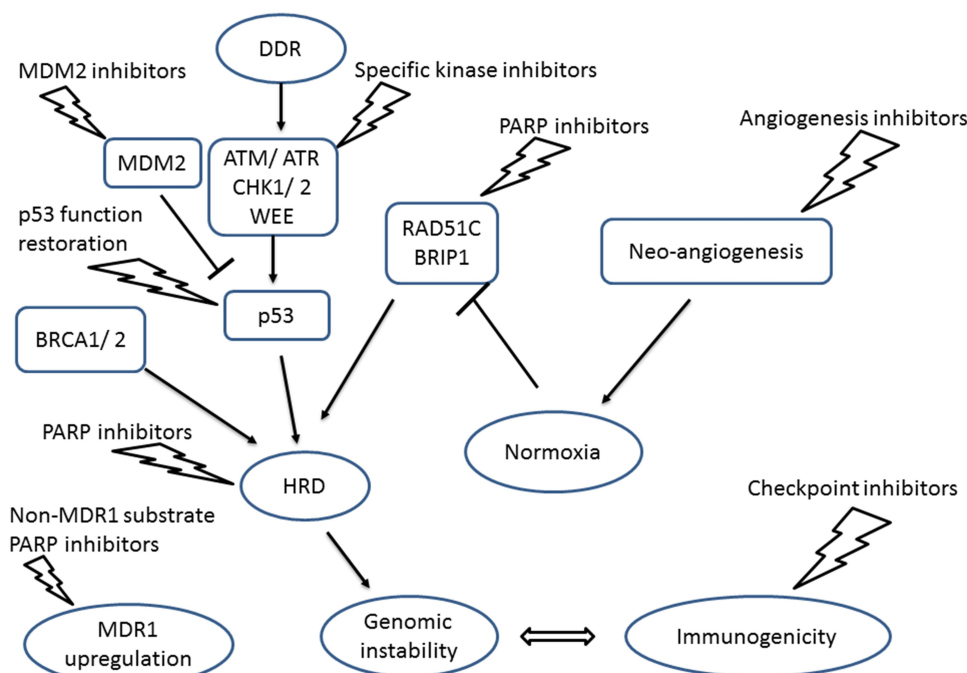


Figure 1 Opportunities of therapeutic interventions based on molecular abnormalities present in high-grade serous ovarian cancers. Lightning bolts represent the specific vulnerability areas that drugs' actions take place.

Abbreviations: DDR, DNA damage response; HRD, Homologous Recombination Deficiency.

Table I Current Indications for PARP Inhibitors in High-Grade Serous Ovarian Carcinomas

Indication	Olaparib	Niraparib	Rucaparib
Maintenance after chemotherapy response		+	
Maintenance after chemotherapy response HRD+	+ (with bevacizumab)		
Recurrent after chemotherapy response	+	+	+
Recurrent BRCA mutant	+		+

CTLA-4 inhibition with a monoclonal antibody synergized with PARP inhibitor veliparib to prolong survival of mice bearing BRCA1-deficient ovarian tumors.²⁴ The effect was mediated by promotion of interferon γ production by immune cells. Ovarian cells proficient for BRCA1 were not sensitive to the combination. Moreover, synergism was specific to CTLA-4 inhibition in this model as veliparib combination with PD-1 or PD-L1 monoclonal antibodies had not any effect in prolonging mice survival compared to controls.²⁴ However, human ovarian cancers with BRCA mutations exhibit in vivo a tumor microenvironment richer in TILs, a higher number of neoantigens and a higher expression of PD-1 and PD-L1 in lymphocytes of the tumor microenvironment.²⁵ All these factors may contribute to sensitivity to PD-1/PD-L1 inhibitors.²⁵ Initial results of clinical trials of PARP inhibitors with immunotherapies are available and several other trials are ongoing. A Phase I/II study of niraparib and pembrolizumab in 60 HGSOc patients pretreated with platinum drugs and taxanes and several of whom had also received anthracyclines and gemcitabine disclosed a response rate of 18% (90% confidence interval: 11–29%) and disease control rate of 65% (90% confidence interval: 54–75%).²⁶ More than 80% of patients were BRCA wild type or unknown, 64% of patients were negative or unknown for HRD and 27% of patients were PD-L1 negative or unknown. Interestingly, no significant differences were observed in the different biomarker groups, although numbers were small. Median Progression-Free Survival (PFS) was 3.4 months (95% confidence interval: 2.1 months–5.1 months). Another Phase II trial (NCT04034927) in patients with recurrent platinum-sensitive HGSOc (or other histologies if BRCA mutant), who have received an unlimited number of platinum lines, randomizes between olaparib or the combination of olaparib with the CTLA-4 inhibitor tremelimumab. In the maintenance setting after response to first-line chemotherapy, the ongoing Phase III ATHENA trial (NCT03522246) will randomize 1012 patients to rucaparib plus nivolumab or each drug alone or placebos.²⁷ A similar phase III trial (FIRST NCT03602859) randomizes patients at the first-line maintenance setting between the

combination of niraparib and the PD-1 inhibitor dostarlimab (TSR-042) or niraparib alone.

The combination of PARP inhibitors with anti-angiogenic agents has also been explored. Olaparib in combination with the VEGFR1-3 inhibitor cediranib has been examined in a randomized phase II trial in 90 platinum-sensitive patients with relapsed HGSOc.²⁸ Both patients with germline BRCA mutations and with wild type or unknown BRCA status were included. Compared with patients that received olaparib monotherapy and had a PFS of 8.2 months, patients who received the doublet had a longer PFS of 16.5 months (hazard ratio: 0.50, 95% confidence interval: 0.3–0.83, $p = 0.006$). Median overall survival (OS) was 44.2 months in the combination group and 33.3 months in the olaparib group (hazard ratio: 0.64, 95% confidence interval: 0.36–1.11, $p = 0.11$). In an exploratory subset analysis, the benefit of the combination was noticed to be derived almost exclusively from the subset of patients that had germline wild type or unknown BRCA, while patients with germline mutations had similar survival outcomes in the two groups.²⁸ In a phase III trial (GY004) the combination of olaparib with cediranib showed an equivalent PFS of about 10.3 months to standard of care chemotherapy in relapsed platinum-sensitive patients who carried either BRCA mutations (23.7%) or were wild-type (Table 2).²⁹ GY004 included also a third arm with women that received olaparib monotherapy and had a PFS of 8.2 months.²⁹ The mechanism of action of the combination of olaparib and cediranib in BRCA wild-type ovarian carcinomas may involve down-regulation of the expression of BRCA1, BRCA2 and RAD51 through induction of hypoxia and inhibition of Platelet-Derived Growth Factor (PDGF) signaling, given that, besides VEGFR1-3, cediranib is a PDGF inhibitor.³⁰ This mechanistic insight may explain also the lack of benefit of the combination compared to olaparib monotherapy in BRCA-mutant ovarian cancers. Interestingly, cediranib has prolonged PFS in platinum-sensitive, relapsed ovarian cancer patients, unselected for BRCA mutations, in combination with carboplatin-based chemotherapy compared with

Table 2 Selected Ongoing and Recently Completed Trials of PARP Inhibitors in Combination with Anti-Angiogenic Agents in High-Grade Serous Ovarian Carcinomas

Study (Reference)	Phase and Number of Patients	Setting	Drugs	Results
GY004 (NCT02446600) ²⁹	Phase III, 579 patients	Recurrent, platinum sensitive	Chemotherapy (paclitaxel/carboplatin or gemcitabine/carboplatin or liposomal doxorubicin/carboplatin) Vs Olaparib Vs Olaparib/cediranib	No difference in PFS of the olaparib/cediranib arm versus chemotherapy
ICON9 (NCT03278717)	Phase III, 618 patients	Maintenance in relapsed following response to platinum-based chemotherapy	Olaparib Vs Olaparib/cediranib	Ongoing
COCOS (NCT02502266)	Phase II/III, 680 patients	Recurrent, platinum resistant or refractory	Chemotherapy (paclitaxel or liposomal doxorubicin or topotecan) Vs Olaparib/cediranib Vs Olaparib Vs Cediranib	Ongoing
OCTOVA (NCT03117933) ³²	Phase II, 132 patients	BRCA mutated, platinum resistant	Olaparib Vs Olaparib/cediranib Vs weekly paclitaxel	Ongoing
CONCERTO (NCT02889900)	Single arm phase II, 62 patients	Platinum resistant relapsed	Olaparib/cediranib	Ongoing
PAOLA-I (NCT02477644) ³¹	Phase III, 806 patients	Maintenance following response to first line platinum/taxane	Bevacizumab Vs Bevacizumab/olaparib	Improved PFS with combination including patients with HRD
AVANOVA (NCT02354131) ³³	Phase I/II, 108 patients	Recurrent, platinum sensitive	Phase II: Niraparib Vs Niraparib/bevacizumab	Improved PFS with combination
OVARIO (NCT03326193)	Phase II, 105 patients	Maintenance following response to first line platinum/taxane/bevacizumab	Bevacizumab Vs Bevacizumab/niraparib	Ongoing

chemotherapy alone.¹⁴ Cancers with HRD are more sensitive to chemotherapy, in addition to PARP inhibitors, and, thus, these data support a role of cediranib in interfering with repair. The combination of olaparib with bevacizumab in the maintenance first-line setting in patients responding to chemotherapy with bevacizumab resulted in a PFS benefit compared with bevacizumab monotherapy in the intention to treat population, independently of HRD status.³¹ However, in this case, the benefit seems to be produced in the subset of patients with HRD (defined as a score of 42 or above in the myChoice assay from Myriad Genetics), with and without BRCA mutations, while patients that were proficient for homologous

recombination derived no benefit. Bevacizumab, as a monoclonal antibody blocking VEGF has no direct effect in blocking other pathways and thus, in this case, the olaparib effect is more prominent in patients with HRD. A selection of recent and ongoing trials of combinations of PARP inhibitors with anti-angiogenic therapies is presented in Table 2.^{31–33}

Another opportunity for further improvement of combination therapy is with the addition of antiangiogenic agents as a triplet with PARP inhibitors and immunotherapy. Triplet combination was examined in a Phase I trial combining olaparib, durvalumab and cediranib mostly in patients with various histologies of ovarian cancers with

no BRCA mutations.³⁴ The triplet combination was well tolerated, and a response signal was present with two-thirds of patients deriving clinical benefit. Niraparib is the subject of a phase II trial (OPAL, NCT03574779) in combination with bevacizumab and the PD-1 inhibitor dostarlimab.

Combining olaparib with the specific PI3K α inhibitor alpelisib was feasible and was reported in a phase Ib study to have activity in platinum-refractory ovarian cancer patients who had received 2 to 5 previous lines of therapy.³⁵ Response rate (RR) was 36% (10 of 28 patients), much higher than the RR that would be expected with each of the two drugs as monotherapy in platinum-refractory disease. PI3K inhibition was, thus, suggested to provide a means to sensitize a priori HR proficient patients to PARP inhibition.³⁵

Mechanistic insights have guided trial development of an additional PARP inhibitor, pamiparib. Pamiparib is a novel PARP Inhibitor that, in contrast to other PARP inhibitors, is not a substrate for the efflux pump MDR1. An ongoing phase II trial (PRECISE NCT03933761) enrolls BRCA-mutated patients who have progressed on MDR1 substrate PARP inhibitors, have no BRCA reversion mutations but are positive for ABCB1 promoter fusions. This trial, if positive, will be a good example on how drugs that are not first in class could fill unmet needs in the therapy of specific sub-sets of patients.

p53/MDM2/ATR/WEE1 Inhibitors

The normal function of wild-type tumor suppressor p53 is almost universally debilitated in HGSOC due to point mutations. These produce two patterns of p53 staining by immunohistochemistry (IHC) that may have therapeutic repercussions if the functional defect of mutant p53 could be restored pharmacologically (Figure 1).³⁶ Missense mutations produce a pattern of p53 increased expression in IHC due to the stabilization of the mutant protein that becomes resistant to proteasome-mediated degradation.³⁷ In contrast, nonsense mutations result in the absence of staining, the so-called null pattern, resulting from absence of translation or degradation of the produced truncated mRNA. In the first scenario, a drug restoring the function of mutant p53 would be expected to be effective, while in the latter scenario it would not be effective due to absence of p53 altogether. The caveat is that p53 loss of function is usually monoallelic and additional lesions, usually across the genome with accumulated instability, are present.

Currently, direct restoration of p53 function is an active area of clinical research and early clinical trials of agents that normalize the function of mutant p53 are ongoing. Two ongoing phase II trials examine the drug APR-246, an analogue of PRIMA-1 (p53 Reactivation and Induction of Massive Apoptosis) in refractory ovarian cancer patients, in combination with liposomal doxorubicin (NCT03268382) or carboplatin (NCT02098343). A broader focus of research in the area is in interventions on the p53 pathway, as a way for further destabilizing the defective DNA damage response (DDR). Small molecule kinase inhibitors of cell cycle checkpoint kinases, including CHK1/2, ATM/ATR and WEE1 kinases fall in this category as their target kinases play key roles in cell cycle checkpoint after sensing DNA damage.^{38,39} In addition to DDR, two of these kinases, ATR and WEE1 participate in protecting stalled transcription forks.⁴⁰ Thus, inhibition of their kinase activity may synergize with agents that interfere with DDR processes, as well as produce synthetic lethality in cancers with defective DDR, such as mutated BRCA genes. CHK1/2 inhibitors are in early development in various tumors including ovarian cancers. Most advanced in development is the intravenous inhibitor prexasertib which has completed phase II trial in BRCA wild-type recurrent HGSOC.⁴¹ This study that included 28 patients with a median of 5 previous lines of treatment showed a partial response in eight patients (28%) in the intention to treat population. Cyclin E and cyclin D were evaluated as lead markers of response to prexasertib and it was noticed that four of the eight responding patients had both cyclin E gene copy gains or amplifications and mRNA upregulation.⁴¹ However, several of non-responding patients had also these alterations. In addition, Cyclin D molecular abnormalities were not associated with prexasertib response. Opportunities for further exploration of CHK inhibitors in HGSOC arise from the observation that CHK1 inhibition is synergistic with inhibition of mitotic kinase AURKA.⁴² The CHK1 inhibitor LY2603618 and the AURKA inhibitor alisertib exhibited synergistic effects in vitro in ovarian cancer cell lines, producing cell cycle arrest and inducing apoptosis.⁴³

WEE1 kinase and related kinase PKMYT1 phosphorylate kinase CDK1 preventing the formation of the complex with cyclin B and preventing CDK1 activation which pushes the cell through the G2 phase into mitosis.⁴⁴ Inhibition of WEE kinase abrogates the G2/M checkpoint and promotes premature mitotic entry with accumulating genomic lesions from unrepaired DNA damage. This

could lead to cell death through apoptosis. WEE kinase expression is an adverse prognostic factor in HGSOC.⁴⁵ A WEE1 kinase inhibitor in development in various cancers, including ovarian cancer, is adavosertib (AZD1775). Pre-clinical studies showed that treatment with adavosertib inhibits the growth of ovarian cancer cells in vitro and in vivo.⁴⁶ Clinical development was promoted in p53 mutant ovarian cancer which had the most promising pre-clinical signals and in combination with chemotherapy, as a means for induction of DNA damage synergizing with WEE1 inhibition.⁴⁷ In a phase II trial in 23 platinum-refractory p53 mutant, BRCA1 mostly wild type (21 of 23 patients) ovarian cancer patients, adavosertib in combination with carboplatin led to a PFS of 5.3 months (95% CI: 2.3 months–9.0 months) and an OS of 12.6 months (95% CI: 4.9 months–19.7 months).⁴⁸ Two long-term responders were also observed. These results were deemed positive in this population of refractory patients. A similar larger phase II trial in the refractory setting (NCT02272790) included 94 patients in multiple arms that each combined adavosertib with a different chemotherapeutic (gemcitabine, paclitaxel, carboplatin or pegylated doxorubicin). The study has completed accrual and preliminary results across arms show a response rate of 31.9% (30 of 94 patients) and a disease control rate of 73.4% (69 of 94 patients) both of which are promising in the refractory setting (www.clinicaltrials.gov).

Phase II trials of combinations of adavosertib or an ATR/ATM inhibitor, ceralasertib (also known as AZD6738) with olaparib are currently ongoing in recurrent ovarian cancer (NCT03579316 and NCT03462342) and seek to recruit 70 and 86 patients, respectively. These combinations are supported by pre-clinical in vitro and in vivo data and have a pathophysiologic rationale, given that WEE and ATR kinases participate in fork protection which is one of the mechanisms of resistance to PARP inhibition.^{40,49} Moreover, the combination of olaparib and adavosertib sensitized lung and pancreatic carcinoma cells with KRAS mutations to irradiation through a mechanism of PARP trapping and replication stress, whereas each drug alone was less effective.^{50,51} However, whether radiosensitization synergism of PARP and WEE kinases inhibition remains also at play in cells without KRAS mutations such as HGSOC will need further study. Another challenge for the development of cell cycle checkpoint inhibitors with PARP inhibitors will be tolerability, as DNA repair may become affected even in cells without underlying defects. The maximal tolerated dose

determined in the phase I study of olaparib with adavosertib was 200 mg twice a day for olaparib and 175 mg twice a day or 200 mg daily three weeks out of four for adavosertib and grade 3–4 cytopenias were common.⁵² Of note, responses in this study of 119 patients across solid tumors that included 25 patients with ovarian cancers were observed in less than 20% of patients.

Besides small molecule kinase inhibitors, a different pharmacologic mode to neutralize cell cycle checkpoint kinases is with targeted protein degraders called PROTACs (Proteolysis targeted chimeras).⁵³ These are protein drug constructs that link a target protein to a E3 ubiquitin ligase, facilitating ubiquitination of the target protein for proteasome degradation.^{54–56} A PROTAC targeting WEE kinase has been developed using adavosertib as the targeting entity and functions by linking the kinase to the receptor CRBN that is part of a complex with E3 ligase CRL4.⁵⁷ The construct was confirmed to be effective in degrading WEE kinase and displayed synergistic activity with olaparib in ovarian cancer cell lines in vitro.⁵⁷ It remains to be seen if this compound and other PROTACs which are expected to enter clinical development will keep their promise.

Inhibitors of MDM2, a ubiquitin ligase and negative regulator of p53, could be effective in the minority of HGSOC with wild-type p53. A preclinical study confirmed that two MDM2 inhibitors, nutlin 3 and idasanutlin are more effective in ovarian cancer cell lines with wild-type p53 compared with those ovarian cancer cell lines with mutant p53 in a sulforhodamine B growth inhibition assay.⁵⁸ The combination with olaparib was additive or, occasionally, synergistic in inhibiting p53 wild-type cells. However, in view of the need for intact p53, MDM2 inhibitors are only good candidates for clinical development in a small minority of HGSOC. Moreover, theoretically, cases with nonsense and other truncating mutations of p53 where the transcribed mRNA is degraded creating haploinsufficiency may also be responsive. These types of mutations are common representing, for example, 36.9% of the p53 mutations in TCGA ovarian cancer study.⁵

Targeting Lesions Beyond Classic HRD

Cyclin-Dependent Kinase 12 (CDK12) is a transcriptional CDK with a kinase domain related to a similar domain of cell cycle kinase CDK1.⁵⁹ Together with a related transcription kinase, CDK13, CDK12 has cyclin K as

a regulating partner and the C-terminal domain of eukaryotic RNA polymerase II (RNAPII) as a main target. Cyclin E is also a target of phosphorylation by CDK12 and cyclin E phosphorylation by CDK12/Cyclin K prevents its interaction with CDK2.⁶⁰ CDK12 plays roles in DDR, mRNA splicing and genomic stability.⁶¹ Loss of function is associated with tandem duplications across the genome with a size around 0.3 Mb or alternatively around 3 Mb.⁶² Particularly affected is replication of long genes of more than 45 Kb.⁶³ CDK12 genetic lesions have been detected in several cancers including ovarian cancer where 9% of cases had CDK12 abnormalities in TCGA ovarian cancer study.⁵ Most common CDK12 lesions in ovarian cancer are mutations but amplifications and deletions also occur more rarely. Mutations in CDK12 or suppression of its function are synthetically lethal with MYC amplifications, BRCA defects and transcription factor FLI translocations.^{61,64} Thus, there exist opportunities for targeting genetic lesions of the kinase in ovarian cancers through synthetically lethal interactions in cancers with BRCA defects or MYC amplifications, should CDK12 kinase inhibitors become available.⁶⁵ Interestingly, MYC may promote homologous recombination and PARP resistance in other cancers and blockade of its function may be synthetically lethal with PARP inhibition.^{66,67} Currently, no direct inhibitors of CDK12 with properties compatible with clinical development exist. FLI lesions, that are also possibly synthetically lethal with CDK12, are not common in ovarian cancers. The CDK12 inhibitor dinaciclib sensitized triple-negative breast cancer cells to the PARP inhibitor veliparib, in vitro and in vivo.⁶⁸ CDK12 mutated cancers may be sensitive to PARP inhibitors despite the mutual exclusivity of CDK12 and BRCA lesions, adding CDK12 to the growing list of DDR genes that confer sensitivity to this class of drugs. This remains to be confirmed in the clinic. In addition, inhibition of CHK1 kinase was proposed as synthetically lethal with CDK12 defects and thus CHK1 kinase inhibitors may be plausible candidates for further targeted therapy development in the CDK12 mutated subset of HGSOC.⁶⁹

Cyclin E, besides being a direct target of CDK12 phosphorylation, has several similarities with CDK12 as a molecular player in HGSOC. Cyclin E lesions, in this case exclusively amplifications, are common and are present in about 20% of HGSOC. They are also mutually exclusive with BRCA mutations and may confer sensitivity to CHK1 or WEE kinase.⁷⁰ Interestingly, another

subset of HGSOC of similar size with the cyclin E amplified subset has been identified having cyclin E over-expression without gene amplification.⁷⁰ Cyclin E over-expression is compatible with BRCA mutations. The mechanism of increased cyclin E protein expression in these cancers is proposed to be over-expression of deubiquitinase USP28 which stabilizes cyclin E. In contrast, cyclin E amplified cases have commonly associated down-regulation of ubiquitin ligase FBXW7 that contributes to protein stabilization, similarly to USP28 up-regulation.⁷⁰ Another similarity of CDK12 and cyclin E lesions as molecular targets in HGSOC is that no specific inhibitor of cyclin E or the associated kinase CDK2 is currently in clinical development. Non-specific CDK inhibitors have been investigated and one of them, the naturally occurring flavonoid, flavopiridol showed a response rate of 17.5% in combination with cisplatin in a phase II trial in the platinum-resistant recurrent setting.⁷¹ Trials focusing in molecularly defined subsets of patients with cyclin E amplification could be a way forward in the development of flavopiridol or similar inhibitors. Moreover, rational combinations based on the increasing knowledge accumulating from genomic studies of synthetic vulnerabilities may also further advance the field.

Hormonal Therapies and Combinations

HGSOC express hormonal receptors, although, in general, the expression for both ER and PR is lower than that observed in Low-Grade Serous Ovarian Carcinomas.^{3,72,73} Previous clinical studies have shown low rates of responses and disease stabilization with hormonal therapies in HGSOC.¹² Unfortunately, most of these trials were performed in unselected patient populations with no enrichment for the targeted receptors or other biomarkers. Given the expression of the targeted receptors in sub-sets of HGSOC and the long record of safety of the targeting drugs in other cancers, hormonal therapies deserve further evaluation in HGSOC. The strategy that could increase the chances of success of trials of hormonal agents in HGSOC should consider enrichment for the targeted receptor(s) as well as combinations with other targeted drugs based on rational exploitation of molecular defects. For example, the combination of letrozole with the CDK4/6 inhibitor palbociclib was reported to be successful in a HGSOC patient who was positive for ER expression in the tumor and had bi-allelic deletion of the

CDKN2A gene encoding for cell cycle inhibitor p16^{INK2A}.⁷⁴ p16^{INK2A} inhibits the cyclin D/CDK4/6 complex and thus its loss would predict palbociclib sensitivity. A small trial of the combination in ER+ ovarian cancer but without selecting for p16^{INK2A} defects is ongoing (NCT03936270). Interactions of ER signaling and the cell cycle as exposed in breast cancer with the successful development of hormonal therapies in combination with CDK4/6 inhibitors may extend beyond the specific inhibition of these CDKs to other CDKs involved in ovarian cancer pathophysiology and could present opportunities for combinatorial drug development in ovarian cancers expressing the ER. However, CDK4/6 inhibitors may not be the optimal partner of hormonal inhibitors in ovarian cancer because multiple genetic lesions of the CDK/RB/E2F pathway and the up-stream regulators exist in this cancer.⁵ Experience from breast cancer suggests that RB mutations confer resistance to CDK4/6 inhibitors.^{75,76}

Targeting Surface Proteins with Antibody-Drug Conjugates

Antibody-drug conjugates have been successfully developed in hematologic malignancies and among solid tumors in HER2-positive breast and gastric cancer but not in any other cancers to date.^{77,78} The advantage of these types of drugs is that, besides a high and specific expression of the target protein on tumor cell surface, there is no need of the target protein to be critical for carcinogenesis as the target works mainly as a vehicle for the entrance of the conjugate into the cell where the cytotoxic moiety will exert the cytotoxicity effect. In ovarian cancer, a good candidate, well expressed in cancer cell surface, is the Folate Receptor alpha (FR α).⁷⁹ FR α is expressed in normal fallopian tubes and is upregulated in ovarian cancer. Expression may further increase in metastatic sites.⁸⁰ FR α expression may be selected in cancer cells given that folate is a methyl-donor participating in nucleic acid metabolism of highly proliferative cells.⁸¹ The monoclonal antibody-drug conjugate mirvetuximab soravtansine is an anti-FR α -humanized IgG1 antibody linked with a cytotoxic moiety that belongs to the maytansines and is an inhibitor of tubulin assembly. Mirvetuximab soravtansine is under evaluation in HGSOc and has completed phase Ib testing as monotherapy and in combination with bevacizumab or carboplatin.^{82–84} The study of mirvetuximab soravtansine as monotherapy included 46 patients with platinum-refractory high-grade ovarian cancers that

had expression of FR α in at least 25% of cells with an intensity of 2+ or 3+.⁸² Overall response rate was 26% and 39% in patients with three or fewer previous lines of therapy. PFS was 4.8 months. In combination with carboplatin in the platinum-sensitive setting, mirvetuximab soravtansine was still feasible at the full dose and showed a high response rate of 71%, including three of 18 patients with complete response.⁸³ PFS was 15 months. In combination with bevacizumab, mirvetuximab soravtansine was studied in the platinum-resistant setting in patients with expression of FR α and one to eight previous lines of therapy.⁸⁴ Both drugs could be administered in full dose. Overall response rate was 39% including five of 66 patients with complete responses. PFS was 6.9 months. Adverse effects of special interest that were observed in the studies of mirvetuximab soravtansine include ocular toxicity in the form of keratopathy as well as pneumonitis. Prophylactic corticosteroid drops may be effective in reducing eye toxicity.⁸⁵ A phase III trial (FORWARD I, NCT02631876) randomized platinum-refractory HGSOc patients with intermediate to high FR α expression who had received up to three lines of therapy between mirvetuximab soravtansine and chemotherapy (either paclitaxel, pegylated liposomal doxorubicin or topotecan).⁸⁶ Median PFS was not different in the two groups (4.1 months and 4.4 months). In a separate analysis of the sub-group of patients with high FR α expression, PFS and ORR were numerically better in the mirvetuximab soravtansine group, although still differences were not statistically significant. FORWARD I has used a simplified scoring system for classifying FR α expression which may have allowed inclusion of patients with lower expression than intended. Currently, another randomized phase III trial (MIRASOL, NCT04209855) using a more detailed classifying system and allowing only high FR α expression is ongoing.

A monoclonal antibody against FR α without a cytotoxic payload, and, thus, not an antibody-drug conjugate, farletuzumab failed to improve PFS in combination with carboplatin and paclitaxel or docetaxel in a phase III trial of 1100 recurrent, platinum-sensitive ovarian cancer patients.⁸⁷ The study included two arms with different doses of farletuzumab and the higher dose, in a pre-specified analysis, had better survival outcomes compared to placebo specifically in patients with tumor marker CA-125 less than three times above normal. In addition, patients that had minimal drug concentration above the median showed significantly better outcomes than the

placebo group.⁸⁷ CA-125, a mucin family glycoprotein, interferes with antibody-dependent cell cytotoxicity by restricting access of immune cells to the Fc part of the antibody, and thus higher concentrations of this protein could undermine farletuzumab efficacy.^{88,89} These results, although disappointing, provide important clues that may be of value in rational development of other monoclonal antibodies and conjugates.

Anetumab ravtansine is an antibody-drug conjugate targeting mesothelin, a surface protein expressed in 70% of ovarian cancers.⁹⁰ The antibody part of anetumab ravtansine is fully human IgG1 sub-type and the payload belongs, similarly to mirvetuximab soravtansine, to maytansines. Preclinical studies in ovarian cancer cell lines in vitro and ovarian human xenografts in mice in vivo showed efficacy of the antibody-drug conjugate against cancers expressing mesothelin.⁹¹ Moreover, anetumab ravtansine showed synergy with both chemotherapy agents and targeted drugs such as bevacizumab and copanlisib. A phase I trial of anetumab ravtansine in patients with various solid tumors with expansion group in ovarian cancer and mesothelioma disclosed acceptable tolerance of the drug. Response rate in the ovarian cohort was only about 10% of patients and exclusively in patients with higher mesothelin expression (above 66%).⁹² Other antibody-drug conjugates targeting mesothelin, FR α and other surface proteins with high expression in ovarian cancer such as the transmembrane mucin MUC16 (from which CA-125 is derived), tissue factor and TROP2 (Trophoblast antigen 2) are also in early development.⁸¹

Targeted radiotherapeutics are a class of antibody-drug conjugates having a radiation-emitting payload instead of a chemotherapy drug. Such a construct with an antibody targeting mesothelin and the alpha particle emitter thorium-227 is under development.⁹³ Preclinical evaluation confirmed that the conjugate induces DNA damage in cell lines in vitro and suppresses progression of xenografts of various human tumors in mice in vivo. Clinical development has started with an ongoing phase I trial (NCT03507452).

A small number of HGSOE, about 3% of ovarian cancers in the MSK-IMPACT study, have amplifications of the ERBB2 gene.⁹⁴ The umbrella trial NCI-MATCH has included an arm of treatment with the antibody-drug conjugate trastuzumab emtansine (TDM-1) for various primary tumors (excluding breast and gastroesophageal adenocarcinomas for which the drug is standard treatment) with amplification of ERBB2.⁹⁵ Fourteen patients with

gynecologic cancers, mostly serous carcinomas, were included and eight of 10 evaluable patients had stable disease as their best response. An analysis of the number of copies of ERBB2 showed that the probability of response was higher in tumors with higher number of copies of the gene.⁹⁵

Immunotherapy Combinations Beyond PARP Inhibitors and Cellular Immunotherapy

Consistent with the low overall number of mutations in HGSOE the initial experience with checkpoint inhibitor-based immunotherapy has been sobering.⁹⁶ Pembrolizumab monotherapy shows a response rate of less than 10% in recurrent ovarian cancer patients that had received one to six prior lines of therapy.⁹⁷ Responses may be slightly higher in PD-L1 positive tumors, as defined by expression of the ligand in 1% of more of cells, and a few long-term responses are observed.⁹⁸ Similar response rates have been obtained with nivolumab and avelumab monotherapy.^{99,100} In a phase I study of atezolizumab in patients with ovarian and endometrial cancers the response rate in the ovarian cohort was 16.1% (two of 12 patients).¹⁰¹

Combinations of immune checkpoint inhibitors, with or without chemotherapy and other targeted therapies, have been successful in improving outcomes in other cancers resistant to immune checkpoint inhibitors monotherapy.¹⁰² This strategy is also evaluated in ovarian cancer. Preliminary results of a randomized phase II trial of nivolumab with ipilimumab versus nivolumab monotherapy in women with recurrent or refractory ovarian cancer are available.¹⁰³ Response rate was 34.1% in the combination arm and 12.2% in the nivolumab monotherapy arm. PFS and OS were also longer with the combination. The combination of nivolumab with bevacizumab was studied in a phase II trial that enrolled 38 relapsed ovarian cancer patients independently of platinum sensitivity.¹⁰⁴ The overall confirmed response rate was 28.9%. Platinum-sensitive patients seem to have a higher response rate (40%, 95% confidence interval: 19.1–64%) than platinum-resistant patients who had a response rate of 16.7%. Most patients (61.1%) had PD-L1 negative tumors but responses were observed in both PD-L1 positive and negative tumors.¹⁰⁴ Atezolizumab with bevacizumab was evaluated in 20 platinum-resistant ovarian cancer patients in an open-label phase Ib trial.¹⁰⁵ The observed median

PFS was 4.9 months and median OS was 10.2 months. Response rate was 15% and an additional 40% had stable disease.¹⁰⁵

A phase III multinational trial evaluates atezolizumab versus placebo in combination with paclitaxel, carboplatin and bevacizumab in advanced ovarian cancer patients either in the neo-adjuvant setting or after incomplete debulking.¹⁰⁶ The influence of PD-L1 expression on outcomes will also be evaluated. Initial results available currently from a press release of the sponsoring company disclose that the addition of atezolizumab to chemotherapy and bevacizumab did not improve PFS. A similar phase III trial is planned in the platinum-resistant setting with weekly paclitaxel or liposomal doxorubicin as the chemotherapy backbone.¹⁰⁷ The Korean Gynecologic Oncology Group has initiated a phase II study (KGOG 346) of neoadjuvant durvalumab and the CTLA-4 inhibitor tremelimumab together with chemotherapy in stage IIIC and IV ovarian cancer.¹⁰⁸ Patients will continue postoperatively with adjuvant chemotherapy and durvalumab and serial biopsies are incorporated in the trial design in order to study biomarkers of response.

Combinations of immune checkpoint inhibitors with other targeted therapies including other immune checkpoint inhibitors, PARP inhibitors (as discussed in a previous section) and angiogenesis inhibitors present an opportunity to improve results in ovarian cancer by converting the immunogenically cold ovarian cancer micro-environment to one with higher inflammation, by both increasing DNA damage and resulting neoantigen production and increasing immune cell influx.¹⁰⁹

CAR-T (Chimeric Antigen Receptor T cell) cell therapy is another type of immunotherapy that involves ex-vivo engineering of patients' T cells to express T cell receptor constructs that associate antigen-binding regions against antigens expressed on tumor cells combined with intracellular co-activatory molecules and transduction sequences of the CD3 molecule.¹¹⁰ The antigen-binding variable regions consist of both heavy and light chains mounted in one peptide. Transduced T cells are expanded ex vivo and then infused back to the patient to attack tumor cells expressing the antigen without the need for co-stimulation. CAR-T cell therapies have been successfully developed in hematologic B lymphocyte malignancies exploiting antigens that are specifically expressed in B cells such as CD19.^{111,112} In solid tumors, CAR-T cell therapy has not yet entered the clinic as hurdles in development have not been successfully

surpassed. These include identification of appropriate target antigens that are specifically expressed in tumor cell surface and are absent or have low expression in other tissues. Other brakes in the successful development of CAR-T therapies relate to penetration of the CAR T cells to the tumor in sufficient numbers to mount an efficacious attack and to circumvent the immunosuppressive microenvironment of solid tumors.¹¹⁰ In addition, expression of candidate surface antigens targeted by CAR-T cells in solid tumors display higher heterogeneity than antigens in hematologic malignancies.¹¹³ In ovarian cancer, CAR-T cells against surface proteins exploited in antibody-drug conjugates such the FR α and mesothelin, as well as against MUC16, have been in development.¹¹⁴ Early generation CAR T-cell therapy against mesothelin has produced only stable disease in a phase I study that included patients with mesothelioma, pancreatic and ovarian cancers.¹¹⁵ Next-generation CAR T technologies such as armored CAR T cells secreting cytokines to reverse immunosuppression in the tumor micro-environment or multi-specific CAR T cells to address target antigen expression heterogeneity will solve some of these hurdles.

Conclusion

This paper describes several active areas of drug development in HGSOc. These include combinations with PARP inhibitors, as the backbone, other therapies targeting DNA repair defects, antibody-drug conjugates and immunotherapy. Although progress has been made in all these fronts of therapeutic endeavors, a lot remains to be accomplished for these advancements to be translated to effective therapies with a place in patient management algorithms. Treatments in development that most probably will soon become established in the clinic include PARP combinations with anti-angiogenic inhibitors. Moreover, next generation immunotherapies and cellular therapies in combination with other targeted therapies derived from improved molecular understanding of the ovarian cancer pathogenesis and paired with increased opportunities offered by new biotechnologies have started and will undoubtedly continue to improve outcomes of ovarian cancer one patient at a time.

Disclosure

The author reports no conflicts of interest for this work.

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