"Latest Advancements in Ovarian Cancer: The Role of Olaparib in Management".

Module V

Future Directions: Expanding the Role of Olaparib in Ovarian Cancer and Beyond

CONTENT

Introduction

Ovarian cancer (OC) is the eighth most common malignancy globally, accounting for 313,959 cases and 207,252 deaths annually. Although among gynecologic cancers its incidence is third after cervix and uterine, it is responsible for more deaths. The 5-years cause-specifc survival ranges from 20% in stage IV and 40% in stage III to 70% in stage II and 90% in stage I. Although >80% of cases are sporadic and without known hereditary predisposition, about 15–20% of patients have germline mutations. Half of the patients have alterations in genes involved in homologous recombination repair (HRR) pathways, an important DNA damage response (DDR) pathway. Poly (ADP-ribose) polymerase inhibitors (PARPi) have been extensively studied in OC and have demonstrated broad activity in both frst-line and recurrent settings. In frst-line and platinum-sensitive recurrent OC (PSOC), PARPi have shown efcacy in maintenance (as a single agent and with bevacizumab) as well as in combination with chemotherapy. However, due to overlapping toxicities in combination with chemotherapy requiring dose reductions, PARPi are recommended as maintenance therapy only. PARPi have also been evaluated as treatment in recurrent OC with BRCA mutations but this is not the preferred treatment option as recent reports demonstrated a lack of overall survival (OS) benefit. 2 DNA Damage Repair (DDR) Pathways DNA damage occurs constantly in response to internal and environmental factors, and evolution has allowed for robust and overlapping repair mechanisms, to maintain DNA integrity. DNA damage due to various endogenous and exogenous infuences is sensed by the cells, and repair pathways are activated based on the type of damage. Mismatch repair (MMR) pathways are activated in response to replication errors, bulky adducts (pyrimidine dimers produced by ultraviolet [UV] exposure) are repaired by nucleotide excision repair (NER), and singlestrand DNA breaks (SSB) by base excision repair (BER). Poly (ADP-ribose) polymerase (PARP) is an enzyme involved in the repair of SSBs in the BER pathway (Fig. 1). Double-stranded DNA breaks (DSB) are produced if cells are exposed to ionizing radiations or chemotherapy drugs, and may lead to genomic instability. These are usually repaired by either the homologous recombination repair (HRR) pathway, which is a high-fdelity, error-free system as it uses sister chromatids as a template, or by the non-homologous end-joining (NHEJ) pathway, which is more efcient but prone to errors (Fig. 1). Impairment in DSB repair due to germline or somatic alterations or epigenetic silencing of genes involved in the HRR pathway is referred to as homologous recombination defciency (HRD). These pathways are interconnected and work in concert along with cell cycle checkpoints to provide overlapping redundant repair mechanisms to ensure efective repair pathways in case one fails to repair the DNA damage. However, this also allows for an inherent vulnerability as alteration in these pathways by genetic, epigenetic, or other mechanisms can drive malignant transformation in the cells, as in the case of BRCA mutations. This simultaneously presents a mechanism of malignant transformation as well as the potential to harness this inherent vulnerability therapeutically by exploiting synthetic lethality in malignant cells. 2.1 Biomarkers of Homologous Recombination Defciency HRD is widely used as a prognostic and predictive biomarker in the management of OC. Currently, validated assays such as myChoice HRD and FoundationOne CDx measure genomic scars using next-generation sequencing (NGS) and provide a threshold to quantify HRD. These tests have demonstrated good predictive value for PARPi activity in platinum-sensitive OC. However, their application is limited in the relapse setting as they may not be precise in estimating HRD status in platinum resistance.

HRD status is dynamic and can be infuenced by prior therapy and the acquisition of resistance mechanisms. Genomic scars are permanent and tend to persist even when HRR is restored. Therefore, functional assays that can refect the dynamic HRD status by estimating RAD51 loading or BRCA1 promoter methylation are being developed. RAD51 loading on single-stranded DNA is mediated by BRCA2 and is a crucial step in HRR. This is lost if there is any alteration in the HRR pathway upstream of RAD51. Initial assays, such as the REcombination CAPacity (RECAP) test, induce ex vivo DNA damage in fresh tumour tissue by ionizing radiation. HRR profciency is assessed by the cell's ability to repair the damage by staining with RAD51, and RAD51 foci per cell are quantifed by fuorescence microscopy. However, the prerequisite of fresh tumour tissue and ex vivo irradiation makes its clinical use diffcult. To overcome these challenges, an assay utilizing γH2Ax immunostaining to estimate endogenous DNA damage in formalin-fxed parafn-embedded (FFPE) tissue has been developed. This can be performed on treatment-naive as well as post-chemotherapy specimens with low tumour content, thereby providing dynamic HRD monitoring. Although the assay predicted response to platinum therapy, it lacks prospective validation and predictive value for PARPi therapy. Another test that can detect dynamic HRD is the BRCA1 promoter methylation assay. It can be performed on FFPE tissue by digital droplet polymerase chain reaction (ddPCR). Methylation status is altered by treatment and loss of BRCA1 methylation has been shown to restore its activity. However, its utility is limited as BRCA1 methylation is seen in only 15% of patients with OC. These functional tests are promising and can extend the predictive utility of genomic scar assays, but require validation in randomized clinical trials.

Surgery and Adjuvant Chemotherapy

Initial management of OC consists of primary debulking surgery (PDS) followed by adjuvant systemic therapy. The goal of surgery is to remove the tumour completely to ideally no residual disease (R0 resection), as this is the most important factor associated with long-term survival. Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is recommended in cases where optimal cytoreduction is not achievable or the patient is deemed unft due to medical reasons.

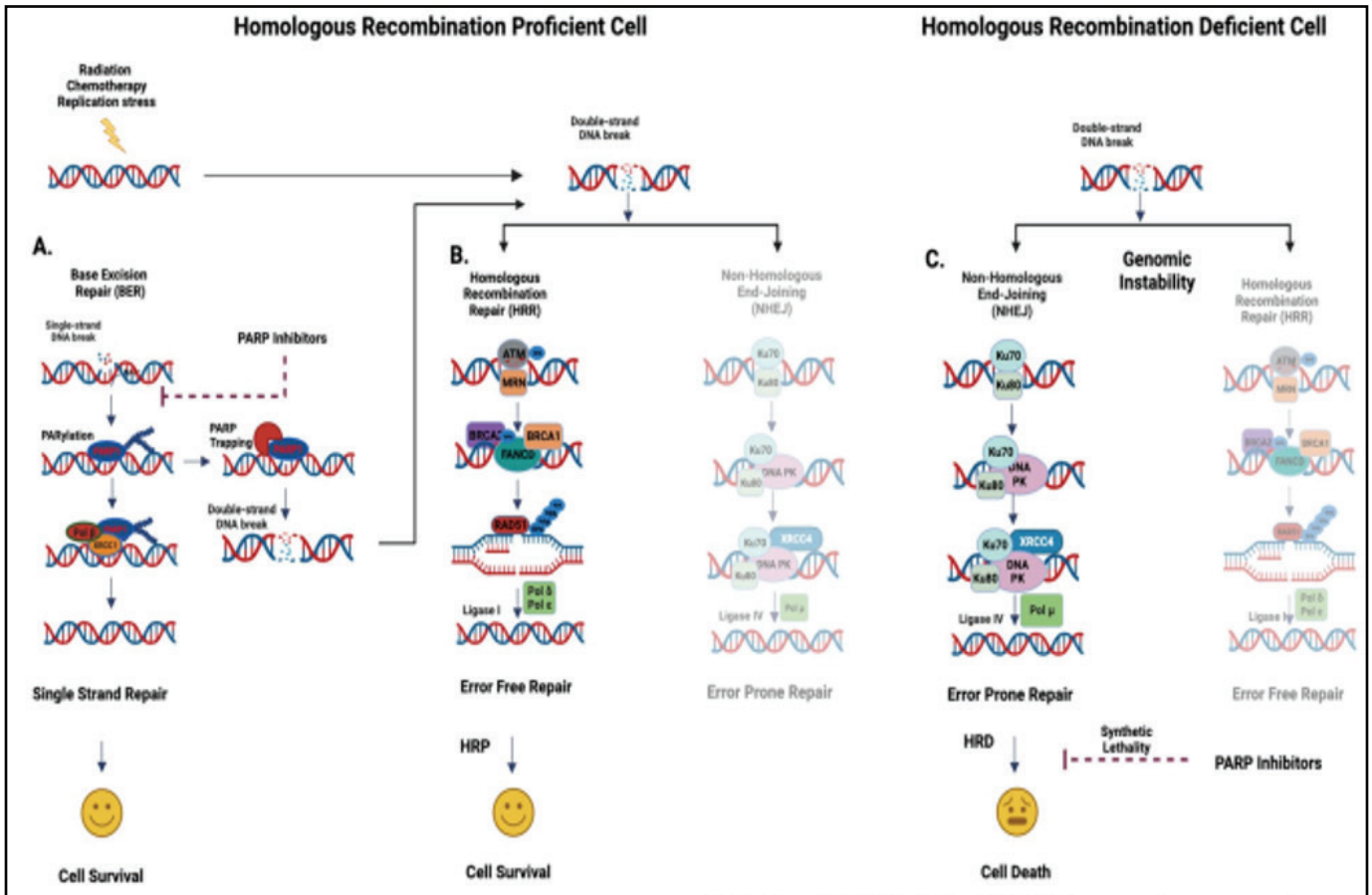

Fig. 1 Mechanisms of DDR. SSB and DSB are introduced in genome in response to external or internal stimuli. **A** BER is the major pathway for the repair of SSB. It involves recognition of SSB and the recruitment of PARP enzymes at the DNA damage site. PARylation is initiated by the transfer of ADP-ribose residues from NAD+ to PARP, relaxes chromatin. DNA polymerase and DNA ligase III are recruited to repair DNA damage. PARP inhibitors promote 'PARP trapping' by blocking PARylation and preventing dissociation of PARP from the SSB site. Unrepaired SSB is converted to DSB. **b** HRR is the predominant pathway for DSB repair in normal cells. The DSB are sensed by the MRN complex, which activate HRR by recruiting various effector proteins such as ATM, BRCA1, BRCA2, RAD51, and FANCD. It is a high-fidelity error-free system as it uses sister chromatids as a template. NHEJ is a secondary pathway that is less active in normal cells and is error prone. **c** In the HRD state, NHEJ becomes the more predominant pathway, and DNA damage is accumulated during the repair process, leading to genomic instability. *BER* base excision repair, *DDR* DNA damage repair, *DSB* double-stranded breaks, *HRD* homologous recombination deficiency, *HRR* homologous recombination repair, *MRN* Mre11-Rad50-Nbs1, *NAD+* nicotinamide adenine dinucleotide, *NHEJ* non-homologous end joining, *PARP* poly (ADP-ribose) polymerase, *PARylation* poly (ADP-ribosyl)ation, *SSB* single-stranded breaks. Created with Biorender.com

Adjuvant chemotherapy is indicated in all patients with advanced OC or early OC with stage IC or II disease, and high-grade histology. Six cycles of carboplatin (area under curve [AUC] 5–6) and paclitaxel (175 mg/m2) administered intravenously every 3 weeks is the preferred regimen. Results from the Gynecologic Oncology Group (GOG) 172 trial favoured adjuvant intraperitoneal chemotherapy in patients with < 1 residual disease post PDS-based, but more recent data from the GOG 252 trial do not support this approach.

Antiangiogenic Agents Bevacizumab is a humanized monoclonal antibody that prevents binding of vascular endothelial growth factor (VEGF) to the endothelial receptors and inhibits tumour angiogenesis [40]. It is the frst targeted therapy to demonstrate improvement in survival in advanced OC. The role of bevacizumab as maintenance therapy in advanced OC was evaluated in two large, randomized trials. In ICON 7, patients with OC post PDS showed progression-free survival (PFS) improvement with maintenance bevacizumab (19.0 months vs. 17.3 months; hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.7–0.9). High-risk patients (stage III with residual disease > 1cm, and inoperable stage III and IV disease) showed significant improvement in both median PFS (15.9 vs. 10.5 months; HR 0.68) and median OS (36.6 vs. 28.8 months; HR 0.64) with bevacizumab. In GOG-0218, patients with newly diagnosed incompletely resected stage III or IV OC showed improved PFS (HR 0.7, 95% CI 0.62–0.82; p <0.001) with maintenance bevacizumab. A post hoc analysis showed improved PFS as well as OS in patients who had ascites at onset. Intrinsic tumour chemosensitivity has been suggested as a marker to better define the population who beneft from bevacizumab. It is measured by cancer antigen (CA)-125 ELIMination rate constant K (KELIM) score, calculated using CA-125 kinetics during the initial 100 days of treatment. Chemosensitive tumours have a KELIM score ≥1.0, while chemoresistance tumours have a KELIM score>1 while chemoresistance tumours have a KELIM score <1 A retrospective analysis of the ICON-7 trial showed that high-risk patients with a KELIM < 1score had better OS (median OS 29.7 vs. 20.6 months; HR 0.78, 95% CI 0.58–1.04: p = 0.09). Findings were confirmed in the GOG-0218 validation study in which patients with a KELIM score <1 showed improved median PFS (9.8 vs. 6.1 months; HR 0.70, 95% CI 0.59–0.82) and OS (36.3 vs. 31.8 months; HR 0.87, 95% CI 0.73–1.03). The highest benefit was observed in high-risk patients with a KELIM score of < 1.

Managing PARP Resistance and Therapies Beyond PARPi

Understanding the mechanism of resistance is the key step before deciding further therapies. The resistant mechanisms discussed above can be targeted to resensitize the resistant OC cells to further therapy. Various modalities (Fig. 3) have been clinically evaluated, including the combination of PARPi with antiangiogenic agents, immune checkpoint inhibitors (ICIs), signal transduction pathway inhibitors, and targeting cell cycle checkpoints. These act by either overcoming resistance by enhancing the activity of PARPi using a combination with other targets in the DDR pathway, or bypassing the resistance mechanism through non-cross resistant therapies. Alternatively, patients who had received PARPi as maintenance may still respond to PARPi rechallenge as monotherapy or as maintenance after chemotherapy.

Rechallenge PARPi

Many patients progress after completion of PARPi maintenance therapy. Thus, the rechallenge strategy has been tried in platinum-sensitive patients who respond to platinum-based chemotherapy, as these patients may not be truly resistant to PARPi. In the Quadra trial, niraparib monotherapy was evaluated in recurrent OC post three or more lines of therapy. Among 37 patients who had received prior PARPi therapy, one patient had a confirmed partial response (3%), and the clinical benefit rate at 16 weeks was 20%. In the OReO trial, relapsed PSOC patients who had received one prior line of PARPi (irrespective of BRCA/HRD status), were randomized to either olaparib or placebo maintenance. PFS was significantly better in the BRCA-mutated cohort (median PFS 4.3 months vs. 2.8 months; HR 0.57, 95% CI 0.37–0.87; $p = 0.022$) as well as the non-BRCA-mutated cohort (median PFS 5.3 months vs. 2.8 months; HR 0.43, 95% CI 0.26–0.71; $p = 0.002$). The results were statistically significant but, clinically, of modest value. The trial suggests that PARPi retain activity in platinum-sensitive relapsed OC, and prior PARPi exposure does not essentially indicate complete resistance to therapy. In the phase II MOLTO study, relapsed high-grade serous OC (HGSOC) patients with germline BRCA mutations were administered with two courses of olaparib maintenance. Patients who did not receive PARPi therapy were treated with platinum-based chemotherapy, followed by olaparib maintenance if they achieved CR/PR after platinum therapy. Patients who had previously received PARPi or who relapsed after receiving initial olaparib were retreated (if they had CR/PR or stable disease to platinum-based therapy) with olaparib (if platinum-free interval ≥ 6 months after initial PARPi therapy) or olaparib with cediranib (if platinum-free interval 6 months in 4 (33%) patients. No new safety concerns were identified with the olaparib rechallenge. There was a significant difference in the duration of first and second olaparib maintenance (12.1 months vs. 4.4 months; $p < 0.001$). Functional HRD evaluation and somatic copy-number alteration (SCNA) assays did not predict PFS after platinum therapy. This study showed that PARPi rechallenge is feasible but it would be difcult to conclude on its efcacy due to small numbers and the lack of a comparator placebo group. Current evidence suggests that PARPi rechallenge is possible in some patients. Fresh tumour biopsy and liquid biopsy may detect BRCA reversion mutation when PARPi are inefective. Further research is ongoing to select appropriate patients and is crucial to optimizing this strategy.

Overcoming PARPi

Resistance Enhancing the PARPi activity by combining it with other agents that can overcome the resistance mechanisms has been extensively studied. This includes targeting angiogenic pathways, cell cycle checkpoints, immune system, and using next-generation PARPi.

Antiangiogenic Agents

Antiangiogenic agents inhibit tumour angiogenesis and cause hypoxia in the tumour. Hypoxic changes in the tumour microenvironment (TME) exert multiple efects, including abnormal DNA damage and repair signals, leading to genetic instability. Inhibition of VEGFR3 also downregulates BRCA1/2 gene expression in the tumour cells. Thus the combination of PARPi with antiangiogenic agents may help overcome resistance. In PSOC, a combination of niraparib and bevacizumab was evaluated in the AVANOVA2 trial. Patients were randomized to either niraparib and bevacizumab or niraparib alone. Improvement in median PFS was observed in the intention-to-treat (ITT) population (11.9 months vs. 5.5 months; HR 0.35, 95% CI 0.21–0.57), bevacizumab-naive patients (14.4 months vs. 6.0 months; HR 0.39, 95% CI 0.22–0.68) and patients without BRCA mutation (11.3 months vs. 4.2 months; HR 0.32, 95% CI 0.17–0.578), but not in patients who were previously exposed to bevacizumab (5.9 months vs. 3.1 months; HR 0.51, 95% CI 0.21–1.26). Cediranib is an oral multikinase inhibitor of VEGF receptors 1–3, and c-kit has been evaluated in recurrent OC but failed to show much promise. In a phase II trial in PSOC or presence of deleterious germline BRCA1/2 mutation, 90 patients were randomized to olaparib with or without cediranib. The median PFS was significantly improved with the combination (16.5 vs. 8.2 months; HR 0.50; p = 0.007) but OS failed to reach statistical significance (44.2 vs. 33.3 months; HR 0.64; p = 0.11). No beneft was seen in a phase III trial evaluating olaparib with or without cediranib and platinum-based chemotherapy in platinum-sensitive relapsed OC. In the EVOLVE trial, a translational phase II study in recurrent OC, patients (irrespective of platinum sensitivity) who had progressed on any prior PARPi received olaparib in combination with cediranib. Although responses were seen in only 8.8% of patients, about 50% were progression free at 16 weeks. Reversion mutations (19%), CCNE1 amplifcation (16%), and ABCB1 upregulation (15%) were common genomic alterations after prior PARPi exposure. 5.2.2 Targeting Cell Cycle Dividing cells transverse through various phases of the cell cycle, viz G1, S, G2 and M. There are certain checkpoints that ensure genetic integrity of the cell while it passes from one phase to another through proteins that act in synergy to regulate this process of transition. The first checkpoint when the resting cell (G1 phase) commits to division is G1/S and is dependent on retinoblastoma (Rb) gene phosphorylation, which in turn is controlled by various cyclins (D and E), cyclin-dependent kinases (CDK) 2 and 4, p16/INK4 and p53. In the S phase, genetic material is duplicated, and in the G2 phase, cells prepare for mitosis by forming various proteins and organelles required in the M phase. G2/M transition is dependent on cyclin B and CDK1 phosphorylation, which is controlled by WEE1, checkpoint kinase (CHK) 1, polo-like kinase 1 (PLK1) and Aurora A. As p53 is universally mutated in serous OC, there is increased reliance on G2/M checkpoint, and blockage at this checkpoint can prevent cell cycle progression and growth of the tumour.

Several cell cycle proteins, including cyclins, CDKs, CHK1 and 2, PLK1, and aurora kinases (Aurora A and Aurora B), are overexpressed in malignancies and are involved in carcinogenesis. Agents that act to inhibit these regulators of cell cycle have been shown to prevent tumour progression.

WEE1 Inhibition

WEE1 is a tyrosine kinase that regulates G2/M checkpoint by inhibiting CDK1 and regulates DNA synthesis in the S phase by inhibiting CDK2. Inhibition of WEE1 by adavosertib (AZD1775) promotes unchecked transition through the G2/M checkpoint, accumulation of damaged DNA, and sensitization to chemotherapy in p53-defcient cells. In a randomized, phase II trial, patients with recurrent platinum-resistant/refractory OC were treated with gemcitabine plus either oral adavosertib or placebo. The adavosertib arm demonstrated significant improvement in objective response rate (ORR; 23 vs. 6%) and median PFS (4.6 vs. 3.0 months; HR 0.55, 95% CI 0.35–0.90). There was also a significant improvement in median OS (11.4 vs. 7.2 months; HR 0.56, 95% CI 0.35– 0.91). In another four-arm, phase II study, two doses of adavosertib were combined with either gemcitabine, paclitaxel, carboplatin, or pegylated liposomal doxorubicin. In all patients, the ORR was 32% and 66.7% in combination with paclitaxel. Both these trials showed that responders were enriched with high CCNE1-amplifed tumours. The IGNITE trial investigated the efficacy of single-agent adavosertib in CCNE1-amplifed (FISH) or overexpressed (IHC) platinum-resistant OC. Results from the cohort with overexpressed CCNE1 showed an ORR of 53%. The efficacy of adavosertib post progression on PARPi was evaluated in the phase II EFFORT trial. Patients were randomized to either adavosertib alone or adavosertib with olaparib, and there was improvement in ORR (29 vs. 23%) and median PFS (6.8 vs. 5.5 months). BRCAwt patients showed improved ORR compared with BRCAm patients in both arms.

ATR Inhibition

ATR plays a very important role in cell cycle by inducing RF stalling, and activates CHK1, cell division cycle 25 (CDC25A/C), and WEE1, which prevents the progression of the cell cycle. ATR inhibition can reverse PARPi resistance due to RF protection by promoting the division of cells with DNA damage [107]. In a phase II trial, patients with recurrent OC (≤ 1 line for platinum resistance) were randomized to gemcitabine with/without berzosertib. The median PFS was signifcantly better in the berzosertib arm (22.9 vs. 14.7 weeks; HR 0.57, 90% CI 0.33–0.98; p = 0.044) [108]. Authors identifed replication stress as an important biomarker of response to gemcitabine. Patients with high replication stress (defned as at least one genomic alteration due to the dysregulated RB pathway and/or oncogene-induced replication stress). Single-agent activity of the oral ATR inhibitor RP3500 in advanced OC was recently demonstrated in the phase I TRESR trial, with an ORR of 25% in patients with synthetic lethal genomic alterations. In the CAPRI trial, olaparib and ceralasertib combination showed an ORR of 46% in patients with BRCAm or HRDpositive PSOC post progression on PARPi.

Checkpoint Kinase Inhibition

CHK1 and CHK2 are kinases regulating the G2/M cell cycle checkpoint by phosphorylating CDC25C and CDC25A. In response to DNA damage, these are activated by ATM/ATR and arrest cell cycle at the G2/M checkpoint to permit DNA damage repair. Prexasertib, a selective inhibitor of CHK1/CHK2, prevents activation of the CHK and allows cell cycle progression under persistent replication stress. It was evaluated as monotherapy in recurrent BRCA wildtype OC in a phase II study.

Partial response was observed in 8/24 evaluable patients (PR 33%), while grade 4 neutropenia was observed in 79% of patients. In another phase II study in platinum-resistant or -refractory OC, PR was seen in 12.1% and 6.9% of patients, respectively. Prexasertib and olaparib combination was studied in a phase I trial in advanced solid tumours. Among 18 patients with BRCA-mutated OC who had progressed on prior PARPi, 4 (22%) had confrmed PR.

POLθ Inhibition

DNA polymerase theta (Polθ) is an enzyme involved in theta-mediated end joining (TMEJ), an error-prone backup pathway of DSB repair. Inhibition of Polθ has shown synthetic lethality in BRCAdefcient cells. ART558 is an inhibitor of Polθ and can reverse PARPi resistance secondary to defects in the 53BP1/Shieldin complex.

Immune Checkpoint Inhibitors

PARPi have synergistic activity in combination with ICIs, primarily via action on the cGAS-cGAMP-STING pathways. PARPi upregulate STING, which promotes the release of proinfammatory cytokines in the TME and also upregulates expression of programmed cell death-ligand 1 (PD-L1) on OC cells. In the phase I/II TOPACIO/KEYNOTE-162 trial in women with recurrent OC or advanced triple-negative breast cancer (TNBC), niraparib was administered in combination with pembrolizumab. Among patients with OC, responses were modest, with an ORR of 18% and a disease control rate (DCR) of 65%. Furthermore, responses were observed irrespective of BRCA, platinum sensitivity, or prior bevacizumab administration.

Next Generation PARPi

AZD5305 is a specific PARP1 inhibitor with better efficacy and safety profile compared with current PARPi. A phase I/IIa PETRA trial is currently evaluating AZD5305 in patients with advanced metastatic ovarian, breast, pancreatic or prostate cancer with loss-of-function mutation in BRCA1/2, PALB2, RAD51C or RAD51D and prior PARPi treatment. Initial reports showed an ORR of 28%. At present, there are limited data to indicate whether second line PARPi are effective at overcoming resistance to first-generation agents.

Bypassing PARPi Resistance

PARPi resistance can be bypassed through targeting non cross-resistant pathways acting independently of HRR. Several approaches have been investigated, including modulating the TME, enhancing drug delivery to tumour cells, and targeting different pathways.

Targeting the Immune System

ICIs have thus far failed to demonstrate meaningful benefit in OC, both in first-line maintenance and in the treatment of recurrent OC. The mechanism of immune resistance in OC is not universal and several genetic, immune, and metabolic factors contribute to establish an immunosuppressive milieu and lack of response to ICIs. T cells infiltrating OC express inhibitory receptors, such as programmed cell death protein 1(PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and lymphocyte activation gene-3 (LAG-3), leading to impaired function of T cells.

Tumour infiltrating CD8-positive T cells secrete interferon-γ, which further upregulates PD-L1 expression on OC cells and macrophages. Additionally, the impact of mutational profile and anatomic sites has been suggested to contribute to the immunosuppressed and hostile TME. However, a recent press release from sponsors of the DUO-O trial suggest significant PFS benefit with the addition of durvalumab to platinum-based chemotherapy and bevacizumab followed by durvalumab/olaparib/bevacizumab maintenance in newly diagnosed advanced OC [128]. DUO-O was a three-arm, placebo-controlled, randomized trial evaluating the efficacy of durvalumab in combination with platinum-based chemotherapy and bevacizumab, followed by maintenance with durvalumab and bevacizumab with or without olaparib in newly diagnosed patients with advanced OC.
In Javelin Ovarian 100, patients with newly advanced OC were randomized to chemotherapy (six cycles of carboplatin/paclitaxel) followed by avelumab maintenance, chemotherapy plus avelumab followed by avelumab maintenance (avelumab combination group), or chemotherapy followed by observation (control group). After interim analysis, the trial was stopped as PFS crossed the futility boundary (median PFS 16.6 months vs. 18.1 months vs. not reached). In Javelin Ovarian 200, recurrent platinum-resistant or -sensitive OC patients were randomized to avelumab, avelumab plus liposomal doxorubicin, or liposomal doxorubicin alone; no benefit was observed in median PFS. In the IMagyn050 trial in newly advanced OC, patients were randomized to atezolizumab or placebo with paclitaxel/carboplatin and bevacizumab; median PFS was 19.5 vs. 18.4 months (HR 0.92, 95% CI 0.79–1.07; p = 0.28) in the overall population and 20.8 vs. 18.5 months (HR 0.80, 95% CI 0.65–0.99; p = 0.038) in the PD-L1-positive population.

In the ATALANTE/ov29 trial, patients with platinum sensitive relapsed OC were randomized to atezolizumab or placebo with chemotherapy and bevacizumab. The median PFS in the overall population was 13.5 vs. 11.2 months (HR 0.83, 95% CI 0.69–0.99; p = 0.041), and 15.2 vs. 13.1 months (HR 0.86, 95% CI 0.63–1.16; p = 0.30) in PD-L1+ patients. Currently, there are many trials exploring adoptive cell therapy, vaccine-based therapies, bispecific antibodies (BiTEs), chimeric antigen receptor therapy (CART), and oncolytic viruses, which may provide opportunities to bypass PARP resistance. Nemvaleukin alfa is an engineered cytokine that selectively binds to the intermediate-affinity interleukin (IL)-2 receptor to preferentially activate and expand CD8+ T cells and natural killer (NK) cells with minimal expansion of CD4+ Tregs. It does not bind to high-affinity receptors due to steric hindrance, thereby avoiding adverse effects associated with it. In a phase I/II trial in multiple solid tumours, nemvaleukin alfa in combination with pembrolizumab showed an impressive ORR of 28.6% (including two complete responses) and a DCR of 71.4% in heavily pre-treated OC patients [133]. ARTISTRY-7 (NCT05092360), a phase III randomized study of nemvaleukin alfa and pembrolizumab versus chemotherapy in platinum-resistant OC is currently recruiting. Ubamatamab is an MUC16/CD3 bispecific antibody. In this first-in-human phase I study in patients with recurrent platinum-resistant OC and elevated CA125, an ORR of 14.3% was observed in those receiving one or more full doses. Maveropepimut-S (DPX-Survivac) is a T-cell-activating vaccine with T-cell epitopes derived from survivin (tumourassociated antigen). In combination with low-dose cyclophosphamide, Maveropepimut-S showed robust T-cell response in OC patients. In the phase I PESCO trial, maveropepimut-S in combination with pembrolizumab and low-dose cyclophosphamide demonstrated tolerable adverse efects, with a response rate of 16% in the initial 24 patients. Similarly, OSE2101 (a multiple-neoepitope vaccine restricted to HLA-A2-positive patients targeting TP53, MAGE2, MAGE3, CEA and HER2) is under evaluation as maintenance therapy (post platinum-based chemotherapy) alone or in combination with pembrolizumab in the TEDOVA trial.

Antibody Drug Conjugates

Antibody drug conjugates (ADCs) are monoclonal antibodies conjugated to a cytotoxic payload that aim to deliver the cytotoxic agents directly to the cancer cells, thereby minimizing the toxicity associated with its systemic exposure. These bind the cell surface antigens and are internalized by endocytosis. The antibodies are selective against tumour-associated antigens and are connected to the cytotoxic agent by a linker that is stable while in circulation but is dissociated after entering the cells. Various antigens of interest in OC that are in clinical trials include folate receptor-α (FRα), NaPi2, tissue factor (TF), mesothelin, MUC16, protein tyrosine kinase 7 (PTK7), and Trop2. Mirvetuximab soravtansine is an ADC against FRα with soravtansine (microtubule inhibitor), as the cytotoxic payload has been studied as a single agent in a recurrent setting as well in combination with chemotherapy and bevacizumab. In the phase III FORWARD 1 trial, patients with platinum-resistant OC who had received one to three prior lines of therapy and had positive FRα expression (≥50% of tumour cells with any FRα membrane staining visible at ≤10× microscope objective) on their tumours were randomly assigned to receive mirvetuximab (6 mg/kg) or chemotherapy. Although the ORR (24% vs. 10%) and CA-125 responses (53% vs. 25%) were improved, there was no difference in terms of PFS in the ITT population (4.1 vs. 4.4 months) as well as high FRα expression (≥75%). In the phase II, single-arm SORAYA trial, patients with platinum resistant OC (PROC) who had received one to three prior lines of therapy and had high FRα expression (≥75% of viable tumour cells exhibiting ≥2+ level membrane staining intensity in the Ventana FOLR1 assay) were enrolled. All patients had received prior bevacizumab and about half of the patients had received prior PARPi therapy.

At a median follow-up of 13.4 months, the ORR was 32.4% (95% CI 23.6–42.2%) and the median duration of response (DOR) was 6.9 months (95% CI 5.6–9.7 months). The most common adverse events (all grade) were blurred vision (41%), keratopathy (29%), and nausea (29%). Mirvetuximab soravtansine was recently granted FDA accelerated approval for platinum-resistant OC patients with high FRα expression. The results differed in the two studies due to variable estimation criteria for FRα expression. In FORWARD1, patients with tumours having any level of expression on tumour cells were included, while in SORAYA, ≥ 2+ level membrane staining intensity was required. An exploratory analysis demonstrated that the predictive biomarker assay in the FORWARD 1 trial did not sufficiently enrich for high folate expressers. Therefore, careful selection of patients is required before considering them for these agents. MIRASOL, a randomized, phase III trial to evaluate the efficacy of mirvetuximab soravtansine compared with chemotherapy (weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan) in PROC (post one to three lines) has completed accrual. FRα testing was performed by the Ventana FOLR1CDx assay and high expression was defined as ≥75% of cells with PS2+ staining intensity. A recent press release by the sponsors reported improved ORR with mirvetuximab soravtansine (42.3 % vs. 15.9 %). Significant improvement in PFS (5.62 vs. 3.98 months; HR 0.65; $p<0.0001$) and OS (16.46 vs. 12.75 months; HR 0.67; $p = 0.0046$) was also reported.

In a phase Ib/II study, mirvetuximab was evaluated in combination with carboplatin and bevacizumab in patients with PSOC with one to two prior lines of therapy. ORR was observed in 81% of patients, with a median DOR of 10.7 months and median PFS of 12.0 months [144]. Mirvetuximab in combination with bevacizumab demonstrated an ORR of 39% and a median PFS of 6.9 months in heavily pre-treated patients with PROC [145]. Similarly, an ORR of 43%, with a median PFS of 5.2 months, was observed in combination with pembrolizumab in PROC with two to four prior lines of therapy.

NaPi2B, a sodium-dependent phosphate transport protein, is expressed in 80–100% of OC cells, but not on normal ovarian tissue. The anti-NaPi2b ADC lifastuzumab vedotin was evaluated in a phase II randomized trial in PROC. A higher ORR was observed compared with liposomal doxorubicin (34% vs. 15%), but PFS was not significantly improved. Another anti-NaPi2b, upiftamab rilsodotin, showed an ORR of 23% in the ITT population and 34% in patients with high NaPi2b expression in pretreated PROC. TF is involved in the extrinsic pathway of coagulation and aberrant expression may be observed in a variety of solid tumours, including epithelial OC. In a phase I/II trial of tisotumab vedotin (ADC against TF) in multiple advanced solid tumours, the ORR in OC patients was 13.9%. Mesothelin is a glycoprotein important for cellular adhesions and is overexpressed in up to 88% of OC patients. Anetumab ravtansine (AR) is a fully human ADC against mesothelin conjugated to a microtubule inhibitor. In a phase II randomized trial in platinumresistant/refractory OC, a combination of anetumab with bevacizumab failed to show any beneft over paclitaxel/bevacizumab. The ORR was 55% with paclitaxel/bevacizumab compared with 18% in the experimental arm. The median PFS was 9.6 months with paclitaxel/bevacizumab compared with 5.3 months with anetumab/bevacizumab (HR 1.7, 95% CI 0.9–3.4).

Modulation of Glucocorticoid Receptors

Cortisol binds to glucocorticoid receptors (GRs) and inhibits cell death by apoptosis, leading to chemotherapy resistance. GRs are abundantly expressed on OC cells and high expression is associated with poor outcomes. Relacorilant is a selective modulator of GRs, which compete with cortisol and can reverse the cortisol-induced chemotherapy resistance in multiple solid tumours. In a phase II, randomized study, recurrent PROC patients were randomized to nab-paclitaxel alone or nab-paclitaxel with intermittent (150 mg/day the day before, of, and after nab-paclitaxel administration) or a continuous schedule of relacorilant (100 mg daily). The intermittent schedule was associated with a significantly improved median PFS compared with nab-paclitaxel alone (5.55 vs. 3.76 months; HR 0.6, 95% CI 0.44–0.98; p = 0.038), but OS failed to reach statistical significance (13.9 vs. 12.2 months; HR 0.67, 95% CI 0.43–1.03; p = 0.066).

Gas6/Axl Signalling

Axl is a receptor tyrosine kinase associated with chemotherapy resistance and poor outcomes in various cancers. It is activated by the binding of its ligand Gas6 (growth arrest specific 6), which acts as growth factor and activates signalling pathways to promote cellular proliferation, invasion, migration, epithelial-mesenchymal transition, angiogenesis, immune evasion, and survival. Axl is expressed on serous OC cells but not on healthy ovarian cells. Batiraxcept (AVB-500) is a fusion protein containing the Fc region of heavy chain immunoglobulin (Ig) G1 fused to the extracellular region of Axl. It acts as a decoy receptor and binds Gas6 with 200-fold high afnity. Batiraxcept was evaluated in phase Ib trial in patients with platinum-resistant OC in combination with paclitaxel or pegylated liposomal doxorubicin. In patients receiving paclitaxel, the ORR was 34.8% and the median PFS and OS was 3.1 and 10.3 months, respectively. GOG-3059/ENGOT OV66 (NCT04729608) is a randomized, phase III study comparing the efcacy of batiraxcept (AVB-S6-500) in combination with paclitaxel in patients with platinum-resistant OC, and is currently recruiting.

G Quadruplex Stabilizers

G-quadruplexes (G4) are transient guanine-rich tertiary structures that are found at promoter sites and telomeric regions in human genome. These are believed to be involved in gene regulation and other processes during cell division, but the precise role of G4 is still undetermined. G4 unwinding proteins/helicases remove these G4 structures in normal cells. Alteration in this process can cause transcriptional changes and DNA breaks, leading to genome instability. HRR is the predominant pathway involved in DNA damage repair in response to G4 alterations. G4-induced genomic instability has been linked to carcinogenesis, although synthetic lethality in this context is being explored as a therapeutic target in HRD cancers. CX-5461 (Pidnarulex) is a G4 stabilizer that promotes tertiary structure and RF arrest, leading to cancer cell death in HRD tumours. It was evaluated in phase I trial in multiple solid tumours and response was observed in 1 (14.2%) patient with BRCA2 mutations among 7 patients with OC. Overall responses were observed in 4/29 patients (ORR 13.8%) with BRCA2 and PALB2 alterations (breast, ovarian, pancreatic cancer). CX-5461 is currently being evaluated in a phase Ib trial in patients with HRD.

Chemotherapy

Chemotherapy remains an option in patients post progression on PARPi. Although there is an overlap between resistance mechanisms of PARPi and platinum, PARPi resistance does not necessarily denote platinum resistance. In ARIEL 4, a phase III study in relapsed OC patients with deleterious germline or somatic BRCA alterations and no prior PARPi, patients were randomized to rucaparib or chemotherapy (based on platinum sensitivity). Fully platinum-sensitive patients (platinum free interval >12 months) were administered platinum-based chemotherapy, while others received weekly paclitaxel. The primary endpoint was investigator assessed PFS in the efficacy population (deleterious BRCA mutations without BRCA reversion mutations). Median PFS was significantly improved with rucaparib in the efficacy population (7.4 months vs. 5.7 months; HR 0.64, 95% CI 0.49–0.84); however, the median OS was better in patients receiving chemotherapy (25.4 months vs. 19.4 months; HR 1.31, 95% CI 0.99–1.72). This was mainly driven by the platinum-resistant subgroup. Similarly, in patients with BRCA reversion mutations, the median PFS was greater with chemotherapy (5.5 months vs. 2.9 months; HR 2.77, 95% CI 0.99–7.76). As crossover was permitted, 80 (69%) patients randomized to chemotherapy crossed-over to rucaparib, while 42.1% of patients in the rucaparib arm did not receive subsequent anticancer treatment. PFS2 (PFS during the first subsequent anticancer treatment) was better in patients crossing over to rucaparib. Furthermore, translational analysis showed that there was a decrease in BRCA reversion mutations in three of four patients randomized to paclitaxel (in the pre- and post-treatment plasma samples). This suggests that paclitaxel may reverse PARPi resistance due to BRCA reversion mutations.

Evolving Clinical Practice

There is a high level of evidence and uniform consensus about the clinical benefit of frontline therapy. However, due to clinician familiarity, there is variation in which agent is most commonly used. Moreover, decisions about sequencing with bevacizumab become more complex(Figure3). In patients with platinum-sensitive disease, only patients with BRCA mutated tumors and who have completed two lines of platinum-based chemotherapy can receive a PARPi, and only olaparib is available in that setting. Caution should be taken when using maintenance PARPi for longer than 24 months, as prior treatment, the patient's age, and duration of PARPi use appear to be the most powerful predictors of risk of MDS/AML. Selection of therapy for potentially platinum sensitive recurrences now depends on more than simply the time since prior platinum and number of prior lines, as the histology and genetic drives are at least as important. We recommend following standardized protocols, such as the NCCN guidelines, for the selection of PARPis and the duration of their usage.

Considerations for Sequencing Olaparib with Other Therapies in the Adjuvant Setting

Olaparib, Radiation, and Endocrine Therapy

With the introduction of new adjuvant treatment options, clinicians are seeking guidance on the sequencing or combining of therapies. Adjuvant olaparib can be given concurrently with endocrine therapy, consistent with the protocol in the OlympiA trial. In cases where radiation is indicated, it is common for radiation therapy to follow chemotherapy. Olaparib must be given at least 2 weeks after completion of radiation therapy, as PARP inhibition has a known radiosensitizing effect. Additionally, per the OlympiA trial protocol, olaparib therapy should be initiated within 12 weeks of completion of the last treatment, which may include surgery, radiation, or chemotherapy. With regard to timing, the CADTH reimbursement recommendation notes that some situations may warrant treatment initiation beyond this 12-week timeframe for certain patients with high-risk breast cancer, such as legacy patients.

Olaparib and Other Adjuvant Treatment Options

Currently, the NCCN Guidelines® suggest that the sequential or combined use of pembrolizumab, olaparib, and/or capecitabine may be considered in select patients with a high risk of recurrence and who meet criteria for treatment with one of more of these agents, although the guidelines also state that there are presently no data on sequencing or combining adjuvant pembrolizumab with olaparib in patients. The absence of combination data represents a key knowledge gap in the treatment of HER2-negative early breast cancer, and various ongoing trials are evaluating the efficacy and safety of concurrent therapies with PARPi treatments including olaparib (Table 5).

Olaparib and Immunotherapy

With recent approvals of both immunotherapy and PARPi treatment in TNBC, there is notable interest in the feasibility of combining these two drug classes. While limited, there is published experience with olaparib in combination with pembrolizumab in patients with breast cancer (see Table 5). Outcomes from these studies suggest that efficacy is unaltered, and that patient toxicity is acceptable with a manageable safety profile. Notably, the ongoing phase II/III KEYLYNK-009 study is evaluating the clinical benefit of pembrolizumab plus olaparib maintenance therapy after first-line chemotherapy with pembrolizumab in locally recurrent inoperable or metastatic TNBC. Results from this study, as well as other trials focusing on sequential/combination therapies, will inform the integration of olaparib with immune-oncology therapies in routine practice.

Olaparib and Abemaciclib

Our search of the literature and ClinicalTrials.gov registry revealed one ongoing National Cancer Institute trial investigating olaparib in combination with abemaciclib in recurrent ovarian cancer (see Table 5). This dose escalation study is examining concurrent use of these two agents.

In this early phase of clinical adoption of olaparib therapy, clinicians have expressed substantial concern regarding the potential cumulative toxicity of this combination; it is anticipated that oncologists will choose either abemaciclib or olaparib, giving consideration to their respective toxicity profiles and duration of therapy. Although the survival benefit observed in the OlympiA trial was in a study population in which only 18% of patients had HR-positive breast cancer, the monarchE trial has not yet reached maturity for its OS analysis. This currently translates in many physicians having a clinical preference for prescribing olaparib for gBRCA-mutated, HR-positive patients.

Olaparib and Capecitabine

There is a paucity of information regarding the sequential use or combination of olaparib with capecitabine. Like abemaciclib, there is concern surrounding potential cumulative toxicity from combined use of capecitabine and olaparib, and it is probable that many oncologists will choose one over the other in practice. Some physicians are also considering sequential use of capecitabine followed by olaparib in patients with high-risk, gBRCA-mutated TNBC, although there are no data to support this strategy.

Table 5. Select Clinical Trials of Olaparib/PARPi Combination Therapy in Breast Cancer and Other Solid Tumours*.

Trial	Population	Intervention	Outcomes
Olaparib and Pembrolizumab in Breast Cancer			
KEYLYNK-0072 [65] (NCT04123366) Phase II, single-arm, open-label study	Previously treated advanced solid tumours with mutations in homologous recombination repair genes *and/or* homologous recombination deficiency (including breast cancer) (N = 168)	• Olaparib 300 mg BID + pembrolizumab 200 mg IV Q3W (35 cycles) until PD or unacceptable AEs	• Grade 3/4 TRAEs, 35.7%; grade 5 TRAEs, 0 • Discontinuations due to TRAEs, 2,4% • Common TRAEs: nausea, 39.3%; anemia, 30.4%; fatigue, 15.5% • Authors noted that "olaparib + pembrolizumab showed promising antitumour activity with manageable safety…"
TOPACIO/KEYNOTE-162 † [66] (NCT02657889) Phase II, single arm, open-label study	Advanced/metastatic TNBC (irrespective of BRCA status or PD-L1 expression) (N = 55)	• Niraparib 200 mg PO daily‡ + pembrolizumab 200 mg IV Q3W	• Most common grade ≥3 AEs: anemia, 18%; thrombocytopenia, 15%; fatigue, 7% • IRAEs: any, 15%; grade 3, 2% • Authors noted that the treatment showed "promising antitumour activity" and a "tolerable safety profile"
KEYLYNK-009 [64] (NCT04191135) Phase II/III, randomized, open-label study	Locally recurrent inoperable or metastatic TNBC (estimated N = 932)	1. Induction pembrolizumab + carboplatin-gemcitabine chemotherapy 2. Maintenance with: - Pembrolizumab 200 mg Q3W + olaparib 300 mg BID; *or* - Pembrolizumab + chemotherapy	• Trial ongoing
NCT05203445 [67] Phase II single-arm, open-label study	Newly diagnosed TNBC or HR+/HER2- BC (N = 23)	• Olaparib 300 mg BID + pembrolizumab 400 mg IV Q6W (x 12 weeks) followed by chemotherapy and surgery	• Trial ongoing
Olaparib and Pembrolizumab in Other Solid Tumours			
KEYLYNK-010 [68] (NCT03834519) Phase III, randomized, open-label study	mCRPC (molecularly unselected) (N = 793)	Arms: • Pembrolizumab 200 mg IV Q3W for ≤35 cycles + olaparib 300 mg PO BID • Abiraterone or enzalutamide daily	• Grade ≥3 TRAEs, 35% vs. 9% • Grade ≥3 IMAEs, 5% vs. 1% • Authors noted that "While pembrolizumab + olaparib resulted in more grade ≥3 TRAEs vs. NHA in patients with previously treated mCRPC, no new safety signals occurred… [69]" • "Most common AEs were anemia, nausea, fatigue, and decreased appetite [69]"
KEYNOTE-365 [70] (NCT02861573) Phase Ib/II, non-randomized, multicohort, open-label study (Cohort A)	mCRPC (molecularly unselected) (Cohort A: N = 102)	Cohort A: • Pembrolizumab 200 mg IV Q3W olaparib 400 mg tab or 300 mg cap PO BID	• Authors noted a "safety profile consistent with the profiles of the individual agents and demonstrated antitumor activity"

Table 5. *Cont.*

Trial	Population	Intervention	Outcomes
ENGOT-OV43/KEYLYNK-001 [71] (NCT03740165) Phase III, randomized, double-blind study	1L ovarian cancer (BRCA non-mutated) (N = 1367)	Arms: • CbT Q3W x 5 cycles + pembrolizumab 200 mg IV Q3W x up to 35 cycles + olaparib 300 mg PO BID starting cycle 7 • CbT Q3W x 5 cycles + pembrolizumab 200 mg IV Q3W x up to 35 cycles + placebo PO BID • CbT Q3W x 5 cycles + placebo IV Q3W + placebo PO BID	• Trial ongoing
KEYLYNK-012 [72] (NCT04380636) Phase III, randomized, placebo- and active-controlled, double-blind study	Unresectable stage III NSCLC (N = 870)	Arms: • Pembrolizumab + CRT followed by pembrolizumab + placebo • Pembrolizumab + CRT followed by pembrolizumab + olaparib • CRT followed by durvalumab	• Trial ongoing
KEYLYNK-013 [73] (NCT04624204) Phase III, randomized, double-blind study	Limited-stage SCLC (N = 672)	Arms: • Pembrolizumab + CRT followed by pembrolizumab + placebo • Pembrolizumab + CRT followed by pembrolizumab + olaparib • Pembrolizumab + CRT followed by placebo	• Trial ongoing
Olaparib and Abemaciclib in Solid Tumours			
NCI-2020-10084 [74] (NCT04633239) Phase I/Ib, open-label, dose escalation study	Recurrent ovarian cancer (N = 42)	• Olaparib PO BID on days 1–28 + abemaciclib PO BID on days 8–28 of cycle 1 and days 1–28 of subsequent cycles • Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity	• Trial ongoing

* Based on a non-systematic search of medical literature and ClinicalTrials.gov based on the following keywords: "olaparib" or "PARP inhibitor" + "pembrolizumab", "abemaciclib", or "capecitabine". † Note: Niraparib clinical trial included. AE, adverse events; BID, *bis in die* (twice daily); cap, capsules; CbT, carboplatin-paclitaxel; CRT, chemoradiotherapy; HRD, homologous recombination deficiency; HRRm, homologous recombination repair mutation; IMAE, immune-mediated adverse events; IRAE, immune-related adverse events; IV, intravenous; mCRPC; metastatic castration-resistant prostate cancer; NHA, next-generation hormonal agent; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-L1, programmed death ligand 1; PO, *per os* (orally); Q3W, every 3 weeks; SCLC, small cell lunger cancer; tabs, tablets; TRAE, treatment-related adverse events; TNBC, triple-negative breast cancer.

Summary Points

1. The recent approval of olaparib in Canada for HER2-negative early breast cancer offers a novel option for personalized treatment of gBRCA-mutated, high-risk early breast cancers. This new indication for olaparib presents a need for early determination of gBRCA status to facilitate systemic therapy planning, as well as surgical decision-making and familial risk identification.

2. Mainstreaming led by oncologists or surgeons offers a potential path to streamlined, patient-centered genetic testing to ensure that results are received in time for treatment decisions. In addition to gBRCA status, the identification of high-risk disease is also critical to personalizing care for patients with HER2-negative breast cancer, as multiple adjuvant therapy options are available for both high-risk TNBC and high-risk HR+/HER2- disease.

3. Capecitabine, olaparib, and pembrolizumab are notable options for high-risk TNBC, whereas abemaciclib, capecitabine, and olaparib are options for high-risk HR+/HER2- disease.

4. Selection between these adjuvant treatments should be guided by the patient's germline BRCA status and the respective criteria for high-risk disease. For patients who are eligible for multiple treatment options, however, there are very limited data to guide the selection, sequencing, or combination of these therapies.

5. Furthermore, recent data presented at the 2023 ASCO Annual Meeting demonstrated that another CDK4/6i regimen, ribociclib with endocrine therapy, shows an IDFS benefit in the adjuvant setting for Stage IB-III early breast cancer.

6. This emerging option may be incorporated into future guidelines and/or algorithms but has not received approval from either the FDA or Health Canada at the time of this publication. PARPi combinations are being explored in a variety of solid tumours, which may provide insights into the safety of these treatment regimens.

7. However, few of these studies focus specifically on early breast cancer, highlighting a need for more trials in this disease setting. Any future trials or real-world evidence examining the combination or sequencing of these therapies, or the comparative efficacy or safety of these treatment options, will provide useful information for evolving the clinical management of early-stage, HER2-negative breast cancer.

8. PARPi resistance has emerged as a major challenge in the management of OC. Ongoing research has provided valuable insight into the mechanisms of resistance to PARPi. Restoration of HRR and RF stability appears to be the major pathways involved. However, it may be difcult to ascertain the exact mechanism in a single patient due to complex interplay between the various pathways. This presents a challenge to develop newer therapies to overcome or bypass the resistance. Multiple trials are currently evaluating the newer agents and combinations targeting these pathways. Further translational research is warranted in this area, with the incorporation of biomarkers to direct the management strategy.

New Treatment Options and Future Directions

Emerging therapies continue to enrich the ovarian cancer treatment arsenal. Beyond PARP inhibitors and combination strategies, newer approaches like antibody-drug conjugates (ADCs) and small molecule inhibitors targeting other DNA repair pathways are under investigation. ADCs like mirvetuximab soravtansine, which targets folate receptor alpha, have shown promise in clinical trials, demonstrating the potential for enhanced efficacy and reduced toxicities.

Practice points

1. PARP inhibitors, along with the potential of combination therapies involving immunotherapy and anti-angiogenic agents, have catalyzed a paradigm shift in ovarian cancer treatment, introducing personalized therapeutic strategies based on genetic profiles.

2. With the approvals of olaparib, niraparib and rucaparib, ovarian cancer patients now have access to tailored therapies that hold the promise of prolonged disease control and improved survival.

3. As emerging treatment options join the armamentarium, the trajectory of ovarian cancer management is poised to witness further advancements in the quest for more effective and targeted therapeutic solutions.

4. Ongoing research seeks to optimize the use of these agents through combination therapies, identification of predictive biomarkers, and understanding mechanisms of resistance.

5. As our understanding of ovarian cancer biology deepens, PARP inhibitors continue to shine as a beacon of hope in the quest for more effective and targeted ovarian cancer treatment options.

For the use or a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

Weston Medical Education Foundation of India

Office No:- 99, 9th Floor, Kalpataru Avenue, Opp. ESIC Hospital,
Kandivali (East), Mumbai - 400101. M: 9322615653 | W: www.wmefi.co.in