Review Article

Narrative review of novel chemotherapeutic agents in management of ovarian cancer

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Abstract: For over 30 years cytotoxic chemotherapy has been used to treat epithelial ovarian cancer. Type of platinum agents, scheduling of chemotherapy and the use of neoadjuvant have been extensively studied. However, in the past decade understanding of the biology of epithelial ovarian cancer and advances in molecular diagnostics have helped to identify new molecular pathways and design small molecules and antibodies which can transform treatment of this deadly disease. Such advances have enabled us to pursue new strategies in order to enhance the efficacy of chemotherapeutic agents, delay recurrence, overcome resistance to platinum or treat platinum resistant disease. In this section we review recent advances leading to approval of new agents, and the current efforts in developing new chemotherapeutic drugs. We discuss the role of antiangiogenic agents including vascular endothelial growth factor (VEGF) antibodies, VEGF receptor (VEGFR) tyrosine kinase inhibitors and Tie-Ang inhibitors. We also review new developments that have led to the approval of poly(ADP-ribose) polymerase (PARP) inhibitors as maintenance therapy in frontline and recurrent epithelial ovarian cancer and discuss new DNA repair targeting agents such as ataxia telangiectasia-mutated and Rad3-related (ATR) and cell cycle checkpoint inhibitors. Finally, we review the study data related to the most recent therapeutic strategies such as antibody drug conjugates. The role of immunotherapy in ovarian cancer has already been discussed in the previous article "The role of immunotherapy in ovarian cancer" in this special series.

Keywords: Ovarian cancer; novel therapies; antiangiogenics; poly(ADP-ribose) polymerase inhibitors (PARP inhibitors); antibody drug conjugates; DNA repair

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Introduction

Advanced epithelial ovarian cancer (EOC) is a deadly disease. Although better surgical skills have improved the outcome for some patients with advance stage disease, surgery alone is hardly considered curative even in patients who are optimally debulked with no residual disease. Therefore, optimisation of cytotoxic chemotherapy has been generally considered as a strategy to improve survival for advanced stage ovarian cancer patients. The standard of care for frontline adjuvant or neoadjuvant chemotherapy in EOC has been chemotherapy with carboplatin and paclitaxel for many years (1,2). However, despite an initial good outcome with frontline chemotherapy, a high proportion of patients develop recurrent disease. Changing the schedule of chemotherapy administration such as weekly administration has not resulted in better survival, and new targets and drugs are urgently needed to improve outcome for patients. In the past few years drugs such as antiangiogenic agents and poly(ADP-ribose) polymerase (PARP) inhibitors have gained regulatory approval either as single agent or combination therapies. However, questions remain unanswered such as the optimum duration of antiangiogenic maintenance therapy, or the target population for various PARP inhibitors. In this article, we review the data and discuss some of the outstanding questions. Additionally, we discuss the new efforts in developing novel therapies for EOC. We present the following article in accordance with the Narrative Review reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-20-58/rc).

Antiangiogenic agents

It is known that overexpression of proangiogenic proteins is associated with peritoneal metastasis and an independent prognostic factor in ovarian cancer (3,4). Therefore, one of the first approaches was to combine chemotherapy with antiangiogenic agents in order to enhance the chemotherapy outcome.

Targeting vascular endothelial growth factor (VEGF)

Bevacizumab is a humanized monoclonal anti VEGF-A antibody, and is the first and the most extensively studied antiangiogenic agent in ovarian cancer. ICON7 and GOG-218 were two pivotal randomised phase 3 studies that investigated addition of bevacizumab to the standard of care carboplatin and paclitaxel followed by maintenance bevacizumab. In ICON7 patients received bevacizumab (7.5 mg/kg) or placebo in combination with carboplatin and paclitaxel every 3 weeks followed by maintenance bevacizumab or placebo for total duration of 12 months (5). Median progression free survival (PFS) was 19.0 months in bevacizumab cohort and 17.3 months in the placebo cohort [hazard ratio (HR), 0.81, P<0.01]. Patients with incompletely debulked stage IIIC or stage IV diseases had larger PFS benefit [median PFS (mPFS) 15.9 *vs.* 10.5 months for bevacizumab and placebo arms, respectively]. In GOG-218 patients were randomised to three arms to receive 6 cycles of carboplatin and paclitaxel every 3 weeks either with bevacizumab (15 mg/kg) followed by maintenance bevacizumab, bevacizumab (15 mg/kg) followed by maintenance placebo, or concomitantly with placebo followed by maintenance placebo, for total duration of 15 months in all three arms (6). The mPFS was 14.1 months in the bevacizumab arm (induction and maintenance) compared to 11.2 months in the induction bevacizumab arm and 10.3 months for the placebo arm (induction and maintenance). There was no significant overall survival difference between the three arms after median follow-up of 102.9 months (6).

Although the patients' population, dose and duration of treatment are different between ICON 7 and GOG-218 trials, both studies appear to suggest improved mPFS with addition of bevacizumab. The magnitude of the mPFS benefit, particularly in the absence of significant overall survival benefit has caused controversies, particularly that subgroup analyses of ICON7 was not pre-planned or powered. However, it is generally accepted that the benefit of bevacizumab is more marked in high-risk patients who may also have overall survival benefit from bevacizumab. Data from both trials seem to suggest that the PFS benefit was lost at the time that bevacizumab maintenance terminated, debating whether extending duration of maintenance bevacizumab may lead to more improved PFS. ENGOT-ov15/ AGO OVAR 17 trial is now evaluating the optimum duration of bevacizumab maintenance therapy. From the safety perspective there is an increased rate of adverse events with bevacizumab including higher risk of bleeding, thromboembolic events, gastrointestinal (GI) perforation and fistula. Although some toxicities are serious, but are generally low prevalence (5,6).

Bevacizumab has also been studied in recurrent EOC. The OCEANS trial evaluated the role of bevacizumab in platinum sensitive recurrent ovarian cancer. In this study patients randomised to receive either bevacizumab or placebo in combination with carboplatin and gemcitabine chemotherapy followed by bevacizumab or placebo until disease progression (7). mPFS was 12.4 months for bevacizumab arm and 8.4 months for placebo arm (HR, 0.484; 95% CI, 0.388–0.605; P<0.0001). The objective response rate (ORR) was also improved by addition of bevacizumab (78.5% *vs.* 57.4% for bevacizumab and placebo, respectively; P<0.0001). However, no overall survival benefit was observed. The toxicity profile was consistent with what is expected for the addition of bevacizumab.

AURELIA trial randomised patients with platinum-resistant recurrent ovarian cancer with 2 or fewer lines of prior chemotherapy to either receive chemotherapy of physicians' choice alone or in combination with bevacizumab until progressive disease or intolerable toxicities (8). Bevacizumab dose was either 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks. mPFS was 3.4 months for chemotherapy alone and 6.7 months for bevacizumab and chemotherapy combination (HR, 0.48; 95% CI, 0.38–0.60; P<0.001). The investigators also observed improvement in ORR by addition of bevacizumab (27.3% *vs.* 11.1% for bevacizumab and chemotherapy alone, respectively, P=0.001). The study allowed crossover after progressive disease and although the overall survival benefit was not statistically significant, a subsequent *post-hoc* subgroup analysis of patients who had crossed over from the chemotherapy alone arm to maintenance bevacizumab (40% of patients) showed overall survival advantage (9).

VEGFR inhibition

Another antiangiogenic strategy that has been pursued is blocking of vascular endothelial growth factor receptor (VEGFR). VEGFR tyrosine kinase inhibitors (TKIs) competitively block the intracellular kinase domain and interrupt VEGF signalling pathway. Few drugs in this class have been evaluated in EOC including pazopanib, nintedanib and cediranib.

Pazopanib

Pazopanib is an inhibitor of VEGR1, 2 and 3, c-Kit and platelet-derived growth factor receptor (PDGFR) that inhibits angiogenesis and tumour growth. AGO OVAR-16 trial was a phase III study that evaluated the efficacy of maintenance pazopanib in advanced ovarian cancer after frontline chemotherapy (10). Patients were randomised to receive pazopanib or placebo for 12 months after frontline chemotherapy. mPFS was in favour of pazopanib (17.9 *vs.* 12.3 months for placebo; HR, 0.81; 95% CI, 0.68–0.96; P=0.019). However, there was high rate of adverse events including hypertension (30.8%). Additionally, 33% of patients had dose discontinuation due to adverse events. Pazopanib was also evaluated in recurrent ovarian cancer. A combination of pazopanib and weekly paclitaxel was not superior to paclitaxel alone in women with recurrent ovarian cancer (11). A recent French trial evaluated addition of pazopanib to paclitaxel in recurrent ovarian cancer patients who progressed during bevacizumab maintenance therapy and found that pazopanib was not superior to paclitaxel alone (12).

Nintedanib

Nintedanib is a triple kinase inhibitor of VEGFR, fibroblast growth factor receptor (FGFR) and PDGFR. AGO OVAR-12/LUME Ovar-1 was a phase III trial that investigated the efficacy of nintedanib maintenance in frontline ovarian cancer (13). Patients were randomised to receive 6 cycles of carboplatin and paclitaxel either with nintedanib or placebo for up to 120 weeks. mPFS was 17.3 months in nintedanib arm and 16.6 months in placebo arm (HR, 0.84; 95% CI, 0.72–0.98; P=0.0239). There was no overall survival advantage with nintedanib maintenance therapy (13).

Cediranib

Cediranib is a VEGFR-1, 2, 3 TKI with high selectivity against VEGFR-2. ICON6 clinical trial studied combination of cediranib with platinum-containing chemotherapy in patients with platinum sensitive recurrent ovarian cancer (14). Patients were randomised to either receive chemotherapy followed by placebo maintenance (arm A), chemotherapy and cediranib followed by placebo maintenance (arm B) or chemotherapy and cediranib followed by cediranib maintenance (arm C). Patients could continue treatment for 18 months or until disease progression. The mPFS was 8.7, 10.1 and 11.1 months for arms A, B and C, respectively (P=0.00003). Restricted means overall survival analysis showed 2.7 months survival benefit in favour of cediranib maintenance arm. Although encouraging, a significant proportion of patients discontinued study treatment due to toxicities (48% in arm C, 37% arm B and 17% in arm A). A clinical trial is currently evaluating combination of cediranib and Olaparib in recurrent ovarian cancer.

Targeting Ang-Tie pathway

Angiopoietin 1 and 2 are regulators of angiogenesis through interaction with the tyrosine kinase receptor Tie2. Inhibition of this axis has also been evaluated as an antiangiogenic strategy in EOC.

Trebananib

Trebananib is a peptide-Fc fusion protein that inhibits binding of angiopoietin 1 and 2 to Tie2.

TRINOVA 1 trial was a phase 2 study that randomised patients with recurrent EOC with three or less prior lines of therapy to receive weekly paclitaxel with trebananib or placebo until disease progression or toxicity (15). The mPFS was 7.2 months for trebananib and 5.4 months for placebo arm (HR, 0.66; 95% CI, 0.57–0.77; P<0.001). In TRINOVA 2 trial patients with recurrent EOC with platinum-free interval of 12 months or less were randomised to either receive pegylated liposomal doxorubicin in combination with trebananib or placebo (16). However, addition of trebananib did not result in any improvement in the mPFS. TRINOVA 3 trial evaluated the role of trebananib in the frontline maintenance setting. Advanced EOC patients with International Federation of Gynecology and Obstetrics (FIGO) stage 3 and 4 were randomised to receive standard carboplatin and paclitaxel in combination with trebananib/placebo followed by trebananib/placebo as maintenance (17). No significant difference in the mPFS was observed with addition of trebananib to the standard chemotherapy (mPFS 15.9 and 15.0 months for trebananib and placebo, respectively; HR, 0.93; 95% CI, 0.79–1.09; P=0.36). At the time of writing this article it is unclear if Amgen plan to continue development of

trebananib in EOC.

PARP inhibitors

PARP inhibitors have now been established in the forefront of advanced EOC treatment. To reach to this position, PARP inhibitors have gone through a long journey which has not always been straightforward. Since 2005 when the first publications highlighted the role of synthetic lethality in *BRCA* mutated cell lines (18,19) until now, there has been many challenges in developing PARP inhibitors. The journey for PARP inhibitors originally started in patients with germline *BRCA* mutations, continued with chemotherapy combination trials which were largely intolerable and negative due to toxicities, and then the challenges of identifying biomarkers beyond germline or tumor *BRCA* mutations emerged. In recent years few positive clinical trials have established the role of PARP inhibitors as an essential component of EOC treatment, particularly in the frontline and platinum sensitive recurrent ovarian cancer. Although reviewing details of all clinical trials over a decade journey of PARP inhibition in ovarian cancer is beyond the scope of this review, below we review the most important findings of the last few years mainly in the frontline and maintenance recurrent ovarian cancer.

Recurrent EOC, maintenance setting

Olaparib

Development of PARP inhibitors as maintenance option started in recurrent platinum sensitive ovarian cancer with either germline or somatic *BRCA* mutations with partial or complete response to their last platinum containing chemotherapy. Study 19 was the first randomised study that demonstrated PFS advantage for olaparib maintenance in this setting (20). In this trial patients with platinum sensitive recurrent ovarian cancer with 2 or more lines of prior platinum containing chemotherapy, and a complete or partial response to the most recent platinum containing chemotherapy were randomised to receive olaparib or placebo. Study 19 showed significant improvement in the mPFS with olaparib compared to placebo (8.4 *vs.* 4.8 months for olaparib and placebo, respectively; HR, 0.35; 95% CI, 0.25–0.49; P=0.001). In this study 51% of patients had germline or somatic *BRCA* mutation. The mPFS in the *BRCA* mutant subgroup was 11.2 months with olaparib and 4.3 months with placebo, and in the *BRCA wt* subgroup 7.4 months with olaparib and 5.5 months with placebo. This encouraging result was followed up by a larger confirmatory clinical trial, SOLO 2, in which patients with germline or somatic *BRCA* mutation who had received 2 or greater lines of chemotherapy and had complete or partial response to treatment received maintenance olaparib or placebo (21). The mPFS was 19.1 months with olaparib and 5.5 months with placebo (HR, 0.30; 95% CI, 0.22–0.41, P<0.0001). Although the overall survival in the overall population was not statistically significant, pre-planned overall survival analysis in the germline *BRCA* mutant subgroup showed overall survival of 52.4 months with olaparib *vs.* 37.4 months for placebo (HR, 0.71; 95% CI, 0.52–0.97; P=0.031).

Niraparib

The NOVA trial evaluated the role of niraparib in patients with platinum sensitive recurrent disease with or without germline *BRCA* mutation, who had received 2 or greater lines of chemotherapy and had complete or partial response to treatment (22). Patients were randomised to receive niraparib or placebo no later than 8 weeks from the completion of platinum containing chemotherapy.

The mPFS was improved with niraparib regardless of *BRCA* mutation or homologous recombination deficiency (HRD) status. The greatest benefit was observed in the germline *BRCA* mutant cohort with the mPFS was 21.0 months with niraparib compared to 5.5 months with placebo (HR, 0.27; 95% CI, 0.17–0.41). In the HRD positive cohort which were *BRCA wt* the mPFS was 12.9 with niraparib and 3.8 months with placebo (HR, 0.38; 95% CI, 0.24–0.59; P=0.001), and in the *BRCA wt* group the mPFS was 9.3 with niraparib and 3.9 months with placebo (HR, 0.45; 95% CI, 0.34–0.61; P=0.001).

Rucaparib

In a similar approach AREIL 3 trial also randomised patients with platinum sensitive disease who had complete or partial response to platinum containing chemotherapy [HRD positive, *BRCA* mutant cohort and intention-to-treat (ITT) population] to receive maintenance rucaparib or placebo (23). The mPFS in *BRCA* mutant cohort was 16.6 months in the rucaparib cohort and 5.4 months in the placebo cohort (HR, 0.23; 95% CI, 0.16–0.34; P<0.0001), in HRD positive patients 13.6 *vs.* 5.4 months for rucaparib and placebo, respectively (HR, 0.32; 95% CI, 0.24–0.42; P<0.0001), and in the ITT population, 10.8 months for rucaparib and 5.4 months for placebo (HR, 0.36; 95% CI,

0.30–0.45; P<0.0001).

Frontline ovarian cancer

With the encouraging data from maintenance setting, studies were designed to evaluate the role of maintenance PARP inhibitors in the frontline ovarian cancer setting.

Olaparib

SOLO 1 clinical trial randomised patients with newly diagnosed advanced ovarian cancer with germline or somatic *BRCA1* or *BRCA2* mutation, to receive olaparib or placebo after completion of platinum-based chemotherapy (24). Prior bevacizumab was not allowed. Patients continued on maintenance olaparib/placebo for up to 2 years. In patients with partial response the treatment could continue beyond 2 years. After median follow-up of 41 months the mPFS was not reached in the olaparib arm and was 13.8 months in the placebo arm. Risk of disease progression or death was 70% lower with olaparib compared with placebo (HR for disease progression or death, 0.30; 95% CI, 0.23–0.41; P<0.001). Recently the investigators reported updated PFS data after 5 years of follow-up at European Society of Medical Oncology (ESMO) 2020 virtual meeting (25). As of March 2020 data cut-off, 48.3% of patients on olaparib still had not experienced disease progression compared with 20.5% of patients on placebo. Median disease-free survival was 56.0 months in olaparib arm and 13.8 months in placebo arm. However, SOLO 1 was restricted to *BRCA* mutant patients with no prior bevacizumab exposure and its result may not be implacable to those without *BRCA* mutations or those who are eligible to receive bevacizumab with chemotherapy.

PAOLA 1 study tried to answer those points by randomising patients who had received frontline platinum containing chemotherapy plus bevacizumab followed by maintenance bevacizumab, to either receive Olaparib or placebo as maintenance therapy. Olaparib/placebo was given for 2 years, or longer in patients who had partial response at 2 years, but maintenance bevacizumab was stopped after 15 months total duration of therapy (26). The mPFS in the ITT population was significantly improved in favour of olaparib (22.1 and 16.6 months for olaparib and placebo, respectively; HR, 0.59; 95% CI, 0.49–0.72; P<0.001).

As expected, patients with somatic *BRCA* mutation or those with HRD had the greatest benefit from olaparib compared to placebo. In *BRCA* mutated patients the mPFS was 37.2 months with olaparib and 17.2 months with placebo (HR, 0.31, 95% CI, 0.20–0.47). In patients with HRD positive tumors (including those with *BRCA* mutation) the mPFS was 37.2 months with olaparib and 17.7 months with placebo (HR, 0.33; 95% CI, 0.25–0.45), and in patients with HRD-positive tumors and no *BRCA* mutations, the mPFS was 28.1 months with olaparib group and 16.6 months with placebo (HR, 0.43; 95% CI, 0.28–0.66). The mPFS in patients with HRD proficient tumors was 16.6 months with olaparib and 16.2 months with placebo (HR, 1.00; 95% CI, 0.72–1.35).

Whilst undoubtedly the result of PAOLA 1 is encouraging, lack of olaparib only arm (no bevacizumab) makes it difficult to establish how much of the PFS benefit might be due to bevacizumab. Additionally, as the optimum duration of bevacizumab maintenance is yet to be reported by ENGOT-ov15/AGO OVAR 17 trial, PAOLA 1 result may be impacted if longer duration of bevacizumab if established as the standard of care.

Niraparib

PRIMA trial enrolled patients at high risk of disease recurrence such as patients with stage 4 disease, stage III inoperable or with residual disease after primary debulking, and patients who received neoadjuvant chemotherapy were (27). Patients who had complete or partial response after frontline platinum containing chemotherapy were randomised to receive niraparib or placebo as maintenance therapy for 3 years or until disease progression. The mPFS in the ITT population was 13.8 and 8.2 months for niraparib and placebo arms, respectively (HR, 0.62; 95% CI, 0.50–0.76; P<0.001). Patients with *BRCA* mutation had mPFS of 22.1 months with niraparib compared to 10.9 months with placebo (HR, 0.40; 95% CI, 0.27–0.62). The mPFS in patients with HRD positive tumors (including those with *BRCA* mutation) was 21.9 months with niraparib and 10.4 months with placebo (HR, 0.43; 95% CI, 0.31–0.59; P<0.001), and in patients with HRD-positive tumors and no *BRCA* mutations was 19.6 months with niraparib and 8.2 months with placebo (HR, 0.50; 95% CI, 0.31–0.83). The mPFS in patients with HRD proficient tumors was 8.1 months with niraparib and 5.4 months with placebo (HR, 0.68; 95% CI, 0.49–0.94).

Veliparib

Since the start of clinical development of PARP inhibitors several attempts were made to combine them with various chemotherapy regimens. However, high grade toxicities mainly myelosuppressive adverse events stopped concurrent

administration of PARP inhibitors and chemotherapies, particularly platinum agents. Veliparib has been the only PARP inhibitor that shown combinability with chemotherapy.

In a 3-arm study, VELIA trial randomised patients into three arms to either receive veliparib concomitantly with chemotherapy followed by maintenance treatment, veliparib concomitantly with chemotherapy followed by maintenance placebo, or placebo concomitantly with chemotherapy and in maintenance setting for up to 2 years (28). The mPFS in the ITT population was 23.5 months and 17.3 for veliparib and placebo, respectively (HR, 0.68; 95% CI, 0.56–0.83). The mPFS in the *BRCA* mutation cohort was 34.7 months for veliparib (concomitant and maintenance) and 22.0 months for patients in placebo group (HR, 0.44; 95% CI, 0.28–0.68). The mPFS in patients with HRD positive tumors (including those with *BRCA* mutation) was 31.9 months with veliparib and 20.5 months with placebo (HR, 0.57; 95% CI, 0.43–0.76), and in patients with HRD-positive tumors and no *BRCA* mutations was 22.9 months with veliparib and 19.8 months with placebo (HR, 0.74; 95% CI, 0.52–1.06). The mPFS in patients with HRD proficient tumors was 15 months with veliparib and 11.5 months with placebo (HR, 0.81; 95% CI, 0.60–1.09). The incidence of hematological toxicities were high but the majority of those adverse events happened during the chemotherapy combination, and adverse events during the maintenance period was in line with what is expected of other PARP inhibitors.

Clinical application of PARP inhibitor in the frontline setting

SOLO 1, PAOLA 1, PRIMA and VELIA trials have established the efficacy of PARP inhibitors in frontline EOC treatment. However, due to differences in design and inclusion criteria for each trial, they also bring uncertainties in clinical decision making. SOLO 1 exclusively recruited *BRCA* mutant whilst PAOLA1, PRIMA and VELIA recruited all-comer patients. It is clear that *BRCA* mutant patients derive the largest benefit from PARP inhibitors with HRs between 0.3 to 0.44. Combination of olaparib and bevacizumab in PAOLA1 trial offers the longest mPFS of 37.2 months. However, question remains as to whether every *BRCA* mutant patient is a candidate for bevacizumab-olaparib combination, particularly if not a candidate for bevacizumab therapy. On the other extreme HRD proficient patients have the least benefit from PARP inhibitors and given their associated adverse event profile, the use of PARP inhibitors may be reserved for recurrent setting rather than the frontline therapy. In the frontline setting, American Society of Clinical Oncology (ASCO) guideline recommends that all newly diagnosed stage III and IV high grade serous or endometrioid EOC patients who have had complete or partial response to the first-line platinum-based chemotherapy receive olaparib if they have *BRCA* mutation, or niraparib in all-comers. It also recommends olaparib plus bevacizumab combination to germline or somatic *BRCA* mutation or HRD positive patients with stage III and IV disease who had prior chemotherapy and bevacizumab, resulting in a complete or partial response. The ASCO guideline does not recommend the combination of veliparib and chemotherapy followed by maintenance veliparib due to the lack of evidence that this approach has superiority compared with the switch to maintenance strategy (29).

Other treatment options under development

Antibody drug conjugates (ADCs)

The therapeutic approach involving attaching a cytotoxic molecule to an antibody which can target antigen expressing cell and allows selective delivery of cytotoxic agents has been a successful approach in treatment of some cancers. HER-2 positive breast cancer (ado-trastuzumab emtansine and trastuzumab deruxtecan), Triple negative breast cancer (sacituzumab govitecan) and some haematological malignancies (brentuximab vedotin and polatuzumab vedotin-piiq) are among cancers currently being treated with ADCs. EOC cells express variety of antigens such as folate receptor alpha (FRα), MUC16, NaPi2b, TROP2 and mesothelin, that can be targeted by ADCs. Currently a handful of clinical trials are investigating the safety and efficacy of these agents in EOC.

Targeting FRα

FRα is expressed in 80–96% of EOC cells, particularly serous and endometroid ovarian cancer (30). It is suggested that overexpression of FRα is associated with poor differentiation of the tumour and resistance to chemotherapy (31). Due to these features FRα has been considered as a suitable target for treatment of EOC. Despite some preliminary data, original attempts to target FRα with either a monoclonal antibody (farletuzumab) or a small molecule inhibitor (vintafolide) were unsuccessful (32,33).

Mirvetuximab soravtansine is an ADC consists of a monoclonal antibody against FRα conjugated with the

tubulin-targeting DM4 through a cleavable linker. Following binding to the FRα, antigen mediated endocytosis results in an intracellular accumulation of DM4 which acts as anti-tubulin agent (34). The safety, tolerability and preliminary efficacy of mirvetuximab soravtansine was evaluated in a phase I dose escalation trial (NCT01609556). This study recruited FRα patients with ovarian, endometrial, non-small cell lung cancer (NSCLC), cervical and real cancer. Patients received doses of 0.15 to 7.0 mg/kg body weight on day 1 of 3 weekly cycles. Although there were some concerns regarding the ocular toxicities such as corneal keratopathy and punctate keratitis at the beginning, with the change of dose calculation according to the adjusted ideal body weight (AIBW) and prophylactic eye lubricants the investigators reported reduction in the incidence and severity of ocular adverse events (35,36). Other adverse events such as neuropathy, fatigue and diarrhea were in line with the expected range of other anti-tubulin cytotoxic agents. The ovarian cancer dose expansion cohort of this trial recruited 27 patients with recurrent heavily pre-treated EOC. All patients had to have FRα expression of equal or over 25%. The investigators reported confirmed ORR of 22% (6/27 patients), with complete response in two patients and partial response in four patients. The investigators reported greater antitumor activity in patients with higher FRα expression levels (35). Another cohort expansion included 46 patients with FRα platinum resistant EOC, using the ≥25% cut-off criterion. Patients with maximum 5 lines of prior therapy were eligible to participate. Twenty-four percent of patients (11/46 patients) had primary platinum resistance disease and only received one prior line of platinum therapy. The remaining patients (35/46 patients, 76%) had at least two prior lines of platinum containing chemotherapy. The ORR was reported 26% with the mPFS of 4.8 months. The response rate in this clinical setting was obviously encouraging when compared to the expected ORR from other chemotherapeutic agent, and led to the design of phase 3 FORWARD I trial in platinum resistant EOC (37). This trial enrolled 366 platinum resistant ovarian cancer patients with eligibility criteria including 1–3 lines of prior therapy and ≥50% FRα expression. Patients were randomised in a 2:1 randomisation ratio to either receive mirvetuximab soravtansine 6 mg/kg AIBW on day 1 each 21-day cycle (248 patients) or chemotherapy of physicians' choice (liposomal doxorubicin, topotecan or weekly paclitaxel; 118 patients). The primary endpoint was PFS in both the ITT population and in patients with high FRα. Secondary endpoints were ORR and overall survival. With a median follow-up of 12.5 months the study did not show any improvement in the PFS in the ITT population (mPFS of 4.1 *vs.* 4.4 months for mirvetuximab soravtansine and chemotherapy, respectively; HR, 0.981; P=0.89). Although mPFS was numerically longer in patients who received mirvetuximab soravtansine compared with chemotherapy (4.8 *vs.* 3.3 months, HR, 0.693; P=0.049), the P value was above the pre-specified threshold of 0.25 and therefore statistically not significant. The investigators reported a trend in improvement of overall survival in patients treated with mirvetuximab soravtansine compared with chemotherapy (16.4 *vs.* 12 months, respectively; HR, 0.67; P=0.048), although the data is still immature. Other studies are currently investigating the efficacy of mirvetuximab soravtansine in combination with chemotherapy or bevacizumab, which showed an overall response rate of 39% in a phase IB trial (38).

Another FRα targeting ADC, STRO-002 recently presented the result of a phase I clinical trial in 34 patients with EOC, with overall response rate of 24% (39).

Targeting MUC16

CA125 is the most commonly used serum marker in ovarian cancer. MUC16 is the transmembrane part of the CA125 antigen. Attempts have been made to utilise ADCs against MUC16. The ADC DMUC5754A is a humanized anti-MUC16 monoclonal antibody conjugated to microtubule disrupting agent, MMAE through a protease-labile linker. A phase I study of this ADC in 66 patients with platinum resistant ovarian cancer showed modest activity with one complete response and six partial responses (40). No further development announcement has been made for this ADC. The result of a phase I expansion study of a another MUC16 targeting ADC, DMUC4064A, with anti-mitotic MMAE payload was presented at American Association for Cancer Research (AACR) 2018. The investigators treated 20 platinum resistant ovarian cancer patients with the dose of 5.2 mg/kg IV every 3 weeks. The overall response rate was 45% with mPFS of 5.8 months and duration of response of 4.4 months (41). The main adverse event was ocular toxicities in 75% of patients.

Targeting NaPi2b

NaPi2b is a transmembrane, sodium-dependent phosphate transporter. It is highly expressed in serous ovarian cancer cells. Lifastuzumab vedotin (DNIB0600A) is a humanized anti-NaPi2b monoclonal antibody conjugated to antimitotic agent MMAE. A phase II clinical trial

evaluated the antitumor activity of lifastuzumab vedotin at the dose of 2.4 mg/kg, given intravenously every 3 weeks, compared with pegylated liposomal doxorubicin 40 mg/m^2, given intravenously, every 4 weeks in patients platinum resistant ovarian cancer (n=99). The investigators reported mPFS of 5.3 months for lifastuzumab vedotin compared to 3.1 months for pegylated liposomal doxorubicin (HR, 0.71) regardless of NaPi2B expression (42). The ORR was 34% *vs.* 15%, for lifastuzumab vedotin and liposomal doxorubicin, respectively (P=0.03). Neuropathy was more frequently observed in lifastuzumab vedotin arm compared with pegylated liposomal doxorubicin (11% *vs.* 4%). Recently the result of a phase 1b study of lifastuzumab vedotin in combination with carboplatin AUC6 in patients with platinum-sensitive recurrent ovarian cancer was published demonstrating the safety and tolerability of this combination (43).

Another anti-NAPi2b ADC, XMT1536, with an auristatin payload has also shown some clinical activity in platinum-resistant ovarian cancer. The interim data from a phase I clinical trial was recently reported at the Society of Gynecologic Oncology (SGO) 2020 and demonstrated tolerability and preliminary efficacy with ORR of 35% (44). An updated data presented at ESMO 2020 virtual meeting demonstrated ORR of 34% in patients with ovarian cancer with a disease control rate of 79% (45). In August 2020 the FDA has granted fast track designation for XMT-1536 for the treatment of patients with platinum-resistant ovarian cancer (46).

Targeting mesothelin

Mesothelin is a glycoprotein that is overexpressed in 70–85% of epithelial ovarian carcinomas. Anetumab ravtansine is a novel, selective humanized antibody against anti-mesothelin conjugated to the maytansinoid tubulin inhibitor DM4. Recently a phase Ib study of anetumab ravtansine in combination with pegylated liposomal doxorubicin in patients with recurrent mesothelin-expressing platinum-resistant ovarian cancer demonstrated encouraging results. Investigators reported partial response of 53%, stable disease of 33% and disease control rate of 83% (47). Other clinical trials with anetumab ravtansine are ongoing including a randomized phase 2 study of bevacizumab in combination with either weekly anetumab ravtansine or weekly paclitaxel (48).

Other DNA targeting agents

Targeting ataxia-telangiectasia-mutated and Rad3-related (ATR)

PARP inhibitors work in different ways, but replication-induced DNA damage followed by collapse of replication forks seems to be the main mechanism of action. Such DNA damages can potentially be repaired by an efficient homologous recombination repair machinery. ATR is required for recovery of stalled replication forks (49,50). Combination of PARP and ATR inhibition increases replication stress and apoptosis (51) and provides the mechanistic rational for the combination of PARP inhibitors and ATR inhibition in order to enhance DNA damage and cell death. It has been shown that combined ATR and PARP inhibition can be used as a strategy to overcome PARP inhibitor resistance in ovarian cancer cells (52). A phase I trial of AZD6738 and olaparib presented safety and tolerability of the combination and some preliminary efficacy data (53). Currently a clinical trial of combination of AZD6738 and olaparib in patients with platinum sensitive and platinum resistant recurrent ovarian cancer is enrolling patients (ClinicalTrials.gov Identifier: NCT03462342).

Another ATR inhibitor, berzosertib (M6620), is at clinical development stage either as monotherapy or combination. Recently, the result of a phase 2 clinical trials of berzosertib plus gemcitabine *vs.* gemcitabine monotherapy in platinum-resistant high-grade serous ovarian cancer was published (54). The investigators enrolled patients with recurrent, platinum-resistant high-grade serous ovarian cancer with no more than one line of cytotoxic therapy in the platinum-resistant setting. Patients received intravenous gemcitabine (1,000 mg/m^2) on day 1 and day 8, or gemcitabine plus intravenous berzosertib (210 mg/m^2) on day 2 and day 9, every 3 weeks until disease progression or intolerable toxicity. The mPFS was 22·9 weeks for gemcitabine plus berzosertib and 14·7 weeks for gemcitabine alone (HR, 0.57; 95% CI, 0.33–0.98; P=0.044). The most commonly observed treatment-related and grade 3 or 4 adverse events were neutropenia (47% *vs.* 39% in the combination arm and monotherapy arm, respectively) and decreased thrombocytopenia (6% and 24% in the combination arm and monotherapy arm, respectively). Two treatment related death (1 sepsis in the gemcitabine arm and 1 pneumonitis in berzosertib arm) was reported in this study.

A phase I study of berzosertib alone and in combination

with carboplatin presented at ASCO annual meeting 2020 (55). The study investigators reported the recommended phase 2 dose of berzosertib at 90 mg/m^2 with carboplatin at AUC5. Frequently observed adverse events were neutropenia in 48% of patients (26% grade 3 and 4), thrombocytopenia in 39% of patients (4% grade 3 or 4), and anemia in 57% of patients (4%; grade 3 or 4). Other clinical trials are currently evaluating berzosertib in combination with different cytotoxic agents and checkpoint inhibitors.

Targeting WEE1

Due to P53 mutations most ovarian cancer cells have deficient G1/S checkpoint, making cancer cells to be reliant on G2/M cell cycle checkpoint in order to avoid mitotic catastrophe (56). WEE1, is a tyrosine kinase which regulates the G2/M cell cycle checkpoint by inactivating CDK1 and preventing mitotic entry in response to extrinsic DNA damage. Inhibition of WEE1 can enhance the effect of DNA damaging chemotherapies by abolition of G2/M checkpoint (57).

Adavosertib

Adavosertib (AZD1755) is an ATP-competitive WEE1 inhibitor that reduces downstream phosphorylation of CDK1, causing premature mitosis and sensitizes cancer cells to DNA-damaging agents (58). It is currently being investigated either as monotherapy or combination with various DNA damaging agents in ovarian cancer and other solid or hematological malignancies.

In a randomized phase II trial total of 121 patients with *TP53*-mutant platinum sensitive ovarian cancer were randomised to receive oral adavosertib (225 mg twice daily for 2.5 days/21-day cycle) or placebo, plus carboplatin (AUC5) and paclitaxel (175 mg/m^2), for six cycles or until progressive disease (59). A total of 59 patients received adavosertib and chemotherapy and 62 patients received placebo and chemotherapy. The primary endpoint was PFS by enhanced RECIST v1.1 criteria (ePFS). Median ePFS was 7.9 months for patients on adavosertib and chemotherapy arm and 7.3 months for patients on placebo and chemotherapy (HR, 0.63; 95% CI, 0.38–1.06; two-sided P=0.080). This met the prespecified criterion for superiority of P<0.2. The investigators reported improvement in mPFS of 1.9 month in favour of adavosertib and chemotherapy when standard RECIST was used. The overall response rate was 75% with adavosertib and chemotherapy *vs.* 69% with chemotherapy and placebo. More patients on adavosertib arm had complete response compared with the chemotherapy alone (11.9% compared with 8.9%, respectively). There were some patterns associating the benefit to certain *TP53* mutations, which requires more confirmation in order to identify a possible biomarker (59). Patients on adavosertib and chemotherapy had more side effects including higher rate of diarrhea (adavosertib 75%; *vs.* placebo 37%), vomiting (adavosertib 63%; *vs.* placebo 27%), anemia (adavosertib 53% *vs.* placebo 32%). Grade 3 and above adverse events were also higher in adavosertib arm compared with chemotherapy alone arm (78% *vs.* 65%, respectively).

Prexasertib

Prexasertib is a cell cycle check point 1 and 2 inhibitor. In a proof of concept phase 2 study, patients with recurrent high-grade serous or high-grade endometrioid ovarian carcinoma and negative family history of hereditary breast and ovarian cancer or known *BRCA* wild-type status, were randomised to receive intravenous prexasertib 105 mg/m^2 every 14 days in 28-day cycles (60). Patients continued treatment until disease progression, unacceptable toxicity, or withdrawal of consent. Seventy-seven percent of patients had platinum-resistant or platinum-refractory disease. Investigators reported partial response in 8/24 patients (33% of patients).

The most common grade 3 or 4 treatment-related adverse events were neutropenia (93% of patients), thrombocytopenia (25% of patients), and anaemia (11% of patients) (reference). Eli Lilly has stopped development of prexasertib since 2018.

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Footnote

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