Abstract. Ovarian cancer is the most frequent cause of death from gynaecological malignancy in the Western countries, and differences in outcome among different histological subtypes are being increasingly recognized. It is generally considered as chemosensitive, but resistant clones evolve in the majority of cases, at varying rates. In this brief review, we describe advances in conventional chemotherapy, particularly the use of weekly paclitaxel. We then focus on new promising agents that target certain pathways which drive the genesis and evolution of ovarian cancer; these include poly(ADP-ribose) polymerase (PARP) inhibitors targeting tumor cells deficient in homologous recombination. We also discuss other targets including the folate receptor. Ovarian cancer has also proved to be one of the most sensitive types of cancer to an anti-angiogenic approach and we summarize recent experience using a range of agents.

Ovarian cancer ranks second in incidence among gynaecological malignancies in developed countries, with the majority of patients being diagnosed with advanced disease. During the past three to four decades, the 5-year relative survival has ranged from 92% for patients with localized disease to 27% for those with distant disease (1).

Patients with advanced epithelial ovarian cancer (EOC) should be treated with optimal cytoreductive surgery, together with adjuvant carboplatin–paclitaxel chemotherapy, in view of the chemosensitivity of the disease. Patients with unresectable disease at diagnosis are treated with up-front chemotherapy. The standard first-line treatment includes carboplatin dosed at an area under the curve (AUC) of 6 mg/ml/min (according to the Calvert formula), along with paclitaxel at 175 mg/m² repeated every three weeks (2, 3).

Even though survival rates of patients with advanced disease have improved over the past decade, there is still an urgent need for a more thorough insight into the molecular pathways that drive cancer progression of the several diverse histological subtypes of ovarian cancer.

I. Advances in Standard Chemotherapy

An impressive overall survival benefit was recently reported in patients with advanced disease treated with weekly compared to three-weekly paclitaxel along with carboplatin (4). In this study, patients with advanced disease all received carboplatin dosed using the Calvert formula at AUC 6 mg/ml/min every three weeks, and were randomly assigned to receive weekly paclitaxel (dose-dense) or the conventional three-weekly regimen. The overall survival (OS) at three years was higher in the dose-dense treatment group (72.1%) compared to the conventional treatment group (65.1%; hazard ratio (HR)=0.75, 95% confidence interval (CI)=0.57-0.97; p=0.03). In a recent survival analysis of the same study (5), the benefit was most clearly evident in the patients who underwent suboptimal debulking surgery. The median OS observed for patients with residual disease ≥1 cm was 51.2 (95% CI=40.1-58.3) months with the intensified regimen compared to 33.5 (95% CI=29.3-43.6) months with the standard 3-weekly one (HR=0.75, 95% CI=0.57-0.97; p=0.0027). In patients undergoing optimal debulking surgery, there was no statistically significant survival benefit with the intensified regimen but this may be due to lack of sufficient number of events so far with optimally-debulked patients, and further follow-up is, therefore, necessary since the median OS has not been reached in either arm.
II. Targeting Tumor Angiogenesis

Data from a number of trials has confirmed that anti-angiogenic therapy has an important role to play at various stages of ovarian cancer and this probably relates to the central role played by the key growth factors in the biology of the healthy ovary (6-20).

Anti-angiogenesis in the First-line Treatment Setting

Bevacizumab. A humanized monoclonal antibody, bevacizumab binds the vascular endothelial growth factor (VEGF) and prevents it from binding to its receptor. In the ICON7 trial (6), patients with advanced or metastatic EOC were assigned to carboplatin-paclitaxel, given every three weeks for six cycles, or to carboplatin–paclitaxel plus bevacizumab (7.5 mg/kg), given concurrently every three weeks for five or six cycles and continued for 12 additional cycles or until progression of disease as maintenance. Progression-free survival (PFS) at 42 months of follow-up cycles or until progression of disease as maintenance.

The greatest benefit from bevacizumab was seen in patients at high risk for progression, with PFS at 42 months of follow-up of 14.5 months with standard therapy and 18.1 months when bevacizumab was added, with median OS of 28.8 and 36.6 months, respectively. In a recent subgroup analysis update, patients with stage IV disease and those who had suboptimal debulking surgery had an OS benefit of 4 months when treated with bevacizumab (39 months for the high-risk patients who received bevacizumab compared to 35 months for the control arm). In ICON7, the survival curves demonstrate non-proportionality and the significant benefit of bevacizumab is, therefore, best calculated using a restricted means analysis (7).

In the initial analysis of the parallel US GOG 218 trial, the combination of carboplatin–paclitaxel with bevacizumab followed by bevacizumab maintenance therapy improved PFS but not OS compared to the same regimen without bevacizumab (8).

The differences between GOG 218 and ICON7 may relate to a higher use of bevacizumab at relapse in the USA; interestingly, however, a recent subgroup analysis of GOG 218 also shows an overall survival benefit of 7.8 months for patients with stage IV disease who received bevacizumab (HR=0.72; 95% CI=0.53-0.97). The median OS for patients treated with chemotherapy and bevacizumab was 40.6 months compared to 32.8 months for those treated without bevacizumab (9).

As a result of these data, bevacizumab has been incorporated into the standard-of-care for first-line treatment in some Centres. However, other investigators have instead preferred to use it as part of the treatment strategy for relapsed disease (see below).

Tyrosine kinase inhibitors. Two large randomized trials have recently been concluded with interesting data as follows: Pazopanib is a tyrosine kinase inhibitor which targets the vascular endothelial growth factor receptors (VEGFR) 1, -2 and -3, the platelet-derived growth factor receptor (PDGFR)-α/β, the fibroblast growth factor receptors (FGFR) -1 and -3, and the tyrosine-protein kinase Kit (c-KIT) (10). In the recently presented AGO-OVAR16 study (11), 940 patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who showed no evidence of progression after surgery and five or more cycles of platinum-taxane chemotherapy were randomly assigned at a ratio of 1:1 to receive 800 mg pazopanib once daily or placebo for up to 24 months. The addition of pazopanib extended the PFS by 5.6 months compared to placebo (HR=0.766; p=0.0021). The median time-to-disease progression was improved to 17.9 months with pazopanib compared to 12.3 months with the placebo. In the first interim analysis for OS, there was no difference between the two arms, however, data have yet to mature. Nonetheless, there is concern about the toxicity and serious adverse events seen in patients treated with pazopanib, which notably included hypertension, diarrhea, nausea, headache and fatigue.

Nintedanib is a tyrosine kinase oral inhibitor which targets VEGFR, PDGFR, and FGFR. In a recently presented study, patients with stage IIB-IV ovarian cancer according to the International Federation of Gynecologists and Obstetricians (FIGO) treated with upfront debulking surgery were randomized to receive the conventional chemotherapy (carboplatin–paclitaxel) with either placebo or nintedanib at 200 mg bid (12). In addition to concurrent treatment, nintedanib or placebo was then continued as maintenance therapy for up to 120 weeks. Nintedanib toxicity was manageable, comprising mainly of diarrhea and raised transaminases. After 752 observed events, analysis of the total population showed that patients who received nintedanib had a marginally-longer median PFS (17.3 vs. 16.6 months; HR=0.84; 95% CI=0.72-0.98; p=0.0239).

Interestingly, and for unknown reasons, in both the pazopanib and nintedanib trials, the benefit of these molecules seemed most clear in patients with optimal rather than suboptimal surgery, in contrast to the subgroup analyses of ICON7 and GOG-218 with bevacizumab (6, 8, 11, 12). For example, 85% of the patients in the pazopanib trial had no evidence of residual disease at the time of enrollment (11), while in the nintedanib study, low-risk patients (as defined in ICON-7) treated with the investigational agent and chemotherapy had an impressive PFS of 27.1 months compared to 20.8 months for similar patients on placebo (12).
Anti-angiogenesis in Relapsed Disease

**Bevacizumab.** Supporting the use of bevacizumab in the treatment of patients with relapsed EOC are the data from the OCEANS trial (13). In this phase III study, patients with platinum-sensitive relapsed EOC received carboplatin with gemcitabine with the addition of bevacizumab or placebo until progression. The investigational arm experienced a 4-month prolongation of PFS compared to the arm that received the placebo (median PFS 12.4 vs. 8.4 months; HR=0.484; 95% CI=0.388-0.605; p<0.0001). Interestingly, no OS benefit was observed. Patients in the placebo did receive bevacizumab at subsequent relapse more frequently than in the other arm and this could partly explain the lack of OS benefit.

**AURELIA** was a phase III study which evaluated the impact of adding bevacizumab to single-agent chemotherapy based either on weekly paclitaxel, topotecan or doxorubicin in patients with platinum-resistant EOC (14). The data on OS were recently presented and, probably due partly to the use of bevacizumab at disease progression, did not reveal any OS benefit between the patients treated with chemotherapy alone and those treated with the addition of bevacizumab, at least for the whole group. However, in a subgroup analysis, patients treated with weekly paclitaxel had a median OS of 13 months, which was significantly increased to 22 months with the addition of bevacizumab (15).

**Tyrosine kinase inhibitors.** Cediranib is a potent oral inhibitor of VEGFR1, -2, one -3 that inhibits VEGF signaling. In the ICON6 phase III trial (16), patients with recurrent platinum-sensitive EOC were randomized to three cohorts: platinum-based chemotherapy with placebo maintenance; concurrent cediranib at 20 mg/day during chemotherapy followed by placebo for up to 18 months; or cediranib at 20 mg/day followed by maintenance cediranib. In a restricted means analysis, OS increased from 17.6 to 20.3 months in the concurrent-plus-maintenance cediranib arm over the reference arm, (HR=0.70; p=0.0419). Notably, it was the first time in the treatment of the EOC that a survival benefit was seen with a tyrosine kinase inhibitor. Using restricted means analysis, the PFS for the reference versus the concurrent-plus-maintenance arm demonstrated a 3.1 month difference favoring cediranib (9.4 months vs. 12.5 months) and a PFS benefit was also seen for the concurrent arm (no maintenance) compared to the reference one (with a PFS of 10.1 vs. 11.4 months, respectively). This indicates that cediranib has significant activity when used both during and after chemotherapy. It was, however, clear that the major benefit in OS was due to the maintenance component of cediranib. The toxicity patients derived from the investigational agent included mainly hypertension, diarrhea, hypothroidism, hoarseness, haemorrhage, proteinuria and fatigue.

To assess whether agents of this type can also provide a benefit in patients with recurrent platinum-resistant disease, an ongoing randomized phase IIIB study of weekly paclitaxel with/without pazopanib is underway (17).

**Targeting the angiopoietins.** AMG386 is a novel molecular agent, a peptide-Fc fusion protein which is designed to inhibit angiogenesis by sequestering the angiopoietins (ANG)-1 and -2, thereby preventing their interaction with the endothelium-specific receptor tyrosine kinase TIE2 receptor. Its activity was evaluated in a phase II study (18) in which all patients with platinum-sensitive disease were randomized to receive daily AMG386 at 80 mg/m2 (three weeks on, one week off) and were randomly assigned 1:1:1 to also receive AMG386 at 10 mg/kg (arm A), AMG386 at 3 mg/kg (arm B), or placebo (arm C). The median PFS was 7.2 months (95% CI=5.3-8.1 months) in arm A, 5.7 months (95% CI=4.6-8.0 months) in arm B, and 4.6 months (95% CI=1.9-6.7 months) in arm C; a dose–response trend was observed for median PFS. The HR for arms A and B combined vs. arm C was 0.76 (95% CI=0.52-1.12; p=0.165). In view of the activity of AMG386, a phase III trial, named TRINOVA-1 (19) was conducted. In that study, patients with recurrent EOC were allocated to two investigative arms. Notably, patients previously treated with bevacizumab were not excluded from the trial, although they comprised a small minority (only 5%) of treated patients. The first arm was treated with AMG386 plus paclitaxel and the second with placebo plus paclitaxel. Patients treated with the investigational drug experienced a PFS prolonged by 52%; median PFS was 7.2 months in the AMG386 arm vs. 5.4 months in the control arm (HR=0.66, CI=0.56-0.76; p<0.001). The data regarding OS are expected to mature in 2014, however, an interim analysis revealed a trend towards improved OS of median 19.0 vs. 17.3 months (HR=0.86; p=0.19) in favour of AMG386.

To further assess the potential benefit of AMG386, another study TRINOVA-2 is underway (20). Patients with recurrent platinum-sensitive or resistant EOC are treated with pegylated liposomal doxorubicin (PLD) combined with AMG386 at a dose of 15 mg/kg or PLD plus placebo. Outcome measures are PFS (primary) and OS (secondary).

These data with AMG386 are certainly of interest; a key issue for the future will be the assessment of its activity in patients previously treated with bevacizumab and further clinical experience should be analyzed with this in mind. Following recurrence of disease, the optimal treatment sequence targeting diverse routes of tumor angiogenesis has yet to be defined, but this will be a key question for further randomized studies.

**III. Treatment of Breast Cancer Tumour Suppressor Gene (BRCA) Mutation Carriers**

**BRCA1** and **BRCA2** are tumour suppressor genes that control the repair of genetic alterations throughout cellular division.
Approximately 14% of patients with ovarian cancer carry a germline BRCA mutation; this proportion is higher for those with high-grade serous histology (22.6%). In addition, a minority of patients (7%) in whom no germline BRCA mutation is detected harbour a somatic BRCA mutation (21).

The aberrant expression of BRCA1 and BRCA2 is associated with an intrinsic sensitivity to poly(ADP ribose) polymerase (PARP) inhibitors which inhibit the repair of single-strand DNA breaks during normal DNA replication, leading to accumulation of DNA double-strand breaks at replication forks. Under normal circumstances, these are repaired via the efficient BRCA pathway-dependent homologous recombination mechanism. Tumors lacking BRCA function have to rely on double-strand repair through other means, such as non-homologous end joining; these are error prone and lead to cell death. Such carcinomas are sensitive to PARP inhibitors alone (22). These molecules exploit the ‘synthetic lethality’ phenomenon since they target one gene in a synthetic lethal pair in which the other gene is defective (23).

The activity of single-agent PARP inhibitor in patients with ovarian, breast or prostate cancer carrying a BRCA mutation was first described by Fong et al. in 2009 (22). In a subsequent study, Gelmon et al. showed that PARP inhibitors may also exert substantial antitumor activity in patients with sporadic high grade serous carcinoma, although most responses were seen in patients with platinum-sensitive disease (24). In that study, 46 patients with relapsed disease received olaparib (AZD2281) at 400 mg twice-a-day continuously. Among the 11 responders, 10 (50%) had platinum-sensitive and one (4%) platinum-resistant disease. This relates to the fact that a proportion of sporadic high-grade serous carcinomas have lost BRCA1 or BRCA2 due to somatic mutations or epigenetic events (25).

In a randomized maintenance trial, patients with high-grade serous, platinum-sensitive EOC, whose disease responded to the most recent platinum-based treatment were randomized to receive either olaparib at 400 mg twice daily as a maintenance therapy or placebo (26). The PFS of patients on olaparib reached 8.4 months compared to 4.8 months for those on placebo (HR=0.35; 95% CI=0.25-0.49; p<0.001). In an interim analysis of OS (58% maturity), patients on olaparib had a median OS of 29.8 vs. 27.8 months for those on placebo (HR=0.88; 95% CI=0.64-1.21) (27). Although initially over 60% of patients were of unknown BRCA mutation status, a subsequent analysis of stored blood (and tumor) samples revealed that 51% of cases had a germline/tumor BRCA1/2 mutation. In this subgroup, the benefit in respect of PFS was most obvious. The OS was also improved for the BRCA mutation-positive subgroup, although less so than the PFS, possibly because of a degree of crossover to olaparib in patients initially receiving placebo. The time to second subsequent therapy reached a median of 23.8 months for patients with BRCA mutation on olaparib compared to 15.3 months for those on placebo (HR=0.46; 95% CI=0.30-0.70, p<0.0003). The toxicity related to olaparib involved mainly nausea, fatigue, vomiting and anaemia, but generally treatment was well tolerated.

A phase III trial evaluating the role of olaparib maintenance (first-line) is currently open and recruiting patients with BRCA mutation who are at high risk of experiencing relapse (FIGO stages III-IV). Patients are randomly assigned to receive either olaparib tablets at 300 mg orally twice daily, or placebo, for up to two years or until objective radiological disease progression (28). This trial, and a repeat of the second-line maintenance trial (29), use a new tablet formulation of olaparib, which should prove easier for patients than the capsule, since it involves taking three tablets instead of eight capsules twice a day.

Another novel PARP1 and PARP2 inhibitor, MK4827 (niraparib), was studied in BRCA mutation carriers and in patients with sporadic advanced tumours in a phase I dose-escalation trial (30). In this trial, eight out of 20 (40%) patients with ovarian cancer with BRCA mutation experienced a partial response, including five out of 10 BRCA1/2 mutation carriers with platinum-sensitive disease. The median duration of response was an impressive 431 days. Interestingly, three out of nine patients with BRCA mutation, platinum-resistant disease showed a partial response, whilst one had long-lasting (>120 days) stable disease. One BRCA1 mutation carrier with platinum-refractory disease had stable disease. The response to niraparib was not limited to patients with BRCA mutation but was also reported in sporadic high-grade serous ovarian cancer cases. Two out of 3 patients with platinum-sensitive, and 3 out of 19 (16%) with platinum-resistant high-grade serous ovarian cancer experienced a partial response, whilst 3 (16%) of the latter group had stable disease. Niraparib, is currently being tested in a phase III, randomized, double-blind, placebo-controlled study as maintenance in patients with platinum-sensitive ovarian cancer who have either a germline BRCA mutation or a high-grade serous tumour and who have responded to their most recent chemotherapy containing a platinum agent (31). A key element of this trial will be the validation of a biomarker for homologous recombination deficiency, which could predict efficacy of PARP inhibition in patients with no evidence of BRCA mutation. A similar maintenance trial is also planned for another PARP inhibitor, rucaparib (32).

Finally, another PARP inhibitor undergoing active clinical investigation is BMN673. In a recently presented study, 22 patients with platinum-sensitive, 4 with platinum-resistant, and two with platinum-refractory relapsed EOC were treated with this agent, which was generally well-tolerated (33). Twenty patients had BRCA1 and 8 BRCA2 mutation. The response rate was approximately 50% for
platinum-sensitive and 30% for platinum-resistant patients. Notably, seven patients with BRCA1 mutation experienced a partial response compared to four with BRCA2 mutation. The median duration of response was 26.9 weeks and the median PFS was 32.3 weeks. The maximum tolerated dose of BMN673 is 1 mg/day, which indicates the high potency of this molecule, which had previously been noted in in vitro studies.

The combination of a PARP inhibitor with chemotherapy has so far not shown clear evidence of benefit. In a recently presented study (34), patients with platinum-sensitive recurrent EOC were treated with chemotherapy of carboplatin–paclitaxel along with olaparib and then continued with olaparib maintenance. Patients with germline BRCA mutations treated with olaparib did have a superior PFS (although not OS) but this was almost certainly related to the impact of single-maintenance agent olaparib which had already been established as having efficacy. When response to chemotherapy with olaparib was compared to chemotherapy alone there was no significant difference.

Other combinations based on pre-clinical data, which include PARP inhibitors with anti-angiogenic agents, or phosphoinositide 3-kinase / serine-threonine-specific protein kinase AKT (PI3K/AKT) inhibitors, may prove to be more beneficial than those with chemotherapy, and appropriate studies are now being planned (35, 36).

IV. Targeting Other Molecular Pathways

Interfering with cell-cycle checkpoints. During the progression of the cellular cycle there are certain checkpoints which control the integrity of the dividing cells and the abundance of the appropriate molecular signs that direct cells towards differentiation. Specifically, the cell cycle is regulated by several cyclin-dependent kinases (CDKs) which control checkpoints. In the case of DNA damage, the CDKs halt the cellular cycle at the G1, S, and G2 phases, allowing time for the cell to repair DNA damage or to initiate apoptosis. Selective inhibition of checkpoints in tumour cells may therefore enhance the efficacy of DNA-damaging agents as long as the DNA repair mechanisms of the host are impaired (37).

MK-1775 is a small molecule inhibitor of WEE1, a nuclear tyrosine kinase belonging to the serine/threonine family, particularly involved in regulation of the G2 checkpoint. For tumors that harbour mutation of p53 gene, which is a tumor-suppressor gene that mainly governs the G1 checkpoint, the S and G2 checkpoints are crucial for differentiation (38). MK-1775 inhibits WEE1 activity by inhibition of the phosphorylation of its direct substrate. Thus, cancer cells harbouning p53 mutation should undergo apoptosis, given that the WEE1-dependent checkpoint is also by passed (39). The hypothesis suggesting that MK-1775 potentiates the activity of cytotoxic agents or radiotherapy has been tested in tumour cell lines such as in human sarcomas, melanoma, neuroblastoma, glioblastoma and pancreatic xenografts (40-44).

In the clinical setting, the ongoing MK-1775 trial is investigating the efficacy, safety, pharmacokinetics, and tolerability of MK-1775 in combination with carboplatin–paclitaxel in patients with relapsed platinum-sensitive, p53-mutant ovarian cancer (45).

Targeting the Folate Receptor (FR). The FR is commonly expressed in more than 80% of epithelial carcinomas, including ovarian cancer. One rationale for targeting the FR is that folic acid may be used as a vector to which a cytotoxic agent is conjugated in order to penetrate the tumor cell, maximizing its antitumor effect, and eventually minimizing toxicity (46).

In a phase II study, 100 out of 149 patients with recurrent platinum-resistant EOC were treated with vintafolide (EC145), which is a folate–desacetylvinblastine monohydrizide conjugate designed to directly target FR-expressing cells, along with PLD (47). Patients were randomized to receive the investigational drug along with PLD (100 patients) or PLD alone (49 patients). Importantly, a functional evaluation of the FR expression was performed with imaging with etarfolatide. Patients were categorized as FR 100% (all lesions FR-positive), FR 10% to 90% (if at least one FR-positive lesion was identified), and FR 0% (no FR-positive lesions). The median PFS was 5.0 months for the vintafolide group compared to 2.7 months for the single-agent PLD group (HR=0.63, p=0.031). The highest median PFS was observed in patients with 100% FR activity (5.5 vs. 1.5 months, HR=0.38, p=0.013). However, no statistically significant PFS benefit was found for patients with 10%-90% positive lesions or those with 0% positive lesions. Further evidence is expected to emerge from an ongoing larger randomized phase III trial, which is comparing EC145 and PLD in combination vs. PLD in patients with recurrent platinum-resistant EOC (48).

Inhibiting Insulin-like Growth Factor (IGF). Another tyrosine kinase receptor whose activation enhances tumorigenesis is the receptor for IGF (49, 50). The IGF family plays a crucial role in the development, progression, and dissemination of multiple cancer types (51). The activation and the increased expression of the receptor 1 of the IGF correlates to the pace and prognosis of the disease. Activated AKT in turn activates the mammalian target of rapamycin (mTOR) pathway, which promotes cell growth and survival, production of transcription factors, and protein synthesis, and regulates the cell cycle (52, 53).

OSI-906 is a low-molecular weight TKI of both insulin receptor and IGF1R, which in turn regulates AKT signaling. In a phase I trial of OSI-906 in patients with recurrent EOC
in combination with paclitaxel, five out of 29 patients experienced a partial response and 11 had stable disease (54). A phase I/II study evaluating OSI-906 in combination with weekly paclitaxel in patients with recurrent EOC recently closed and results are awaited (55).

**IV. Treatment Tailored to Histology**

**Low-grade EOC.** Among the diverse histological subtypes of EOC there are certain molecular imprints and distinct genetic abnormalities which may have a predictive impact. For instance, low-grade serous ovarian carcinomas (LGSC) frequently harbour mutations in the Kirsten rat sarcoma viral oncogene (KRAS) or the murine sarcoma viral proto-oncogene homolog B1 (BRAF), and express active mitogen-activated protein kinase (MAPK) (56). Singer et al. reported mutations in BRAF (codon 599) in 33% of LGSC samples and KRAS mutations (codons 12 and 13) in 35% of the cases, mutations which notably were mutually exclusive (57). In the COSMIC database, 39% of LGSC samples had the V600E allele BRAF mutation (58, 59). Further molecular insight revealed that these LGSC do not harbour mutations in p53 (60).

In 2008, Nakayama et al. suggested that in patients with ovarian cancer harbouring KRAS or BRAF mutations, activated ERK1/2 pathway is critical to tumour growth and survival, and these patients may, thus, benefit from agents that inactivate ERK1/2 (61). Recently, in a phase II study (62) patients with recurrent LGSC of the ovary or peritoneum were treated with selumetinib, a potent, selective inhibitor of MEK1/2. Eight out of 52 assessable patients, experienced partial or complete response (15%; 90% CI=7.9-26.1%). Median PFS was 11.0 months (95% CI=3.6-15.9 months) with 33 patients having a PFS of 90% CI=7.9-26.1%).

**Clear Cell EOC.** Clear cell ovarian carcinomas constitute a minority, accounting for only 5-13% of all EOCs (67). Their aggressive behaviour and resistance to conventional chemotherapy mandates a further insight into their biology. The molecular pathways implicated lead to new options for treatment. PI3K is found to be mutated in 33% of patients with clear cell ovarian cancer (68), whilst loss of the phosphatase and tensin homolog (PTEN) gene expression is noted in 40% (69) and amplification of AKT2 was noted in 5/21 samples in a separate study (70). Various inhibitors of the PI3K/AKT pathway are therefore currently in clinical studies and there is anecdotal evidence of efficacy.

In a phase II trial, the addition of temsirolimus to carboplatin and paclitaxel together will be studied in patients with newly diagnosed stage III or stage IV clear cell ovarian cancer (71). An alternative approach, based on similarities in genomic profile between clear cell ovarian and renal cancer (72) involves the antiangiogenic agent sunitinib. This agent is currently being evaluated in patients with persistent or recurrent clear cell ovarian cancer (73).

**Mucinous ovarian carcinoma.** Mucinous ovarian carcinoma is a rare malignancy comprising less than 4% of ovarian cancer cases. It commonly presents as a stage I tumour but when more advanced, the response rate to standard chemotherapy is lower compared to other more common pathological subtypes (74). Interestingly, 20% of mucinous carcinomas were found to express the human epidermal growth factor receptor 2 (HER2) according to immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) criteria (75,76). In a study of 33 cases (76), 5 of the carcinomas (3+ in 4 cases, 2+ in 1 case) had HER2 amplification. Various inhibitors of the PI3K/AKT pathway are therefore currently in clinical studies and there is anecdotal evidence of efficacy.

In a phase II trial of unselected patients with ovarian cancer (77), but further evaluation does seem indicated, specifically in patients with HER2+ mucinous pathology.

**Conclusion**

The development of more sophisticated molecular agents targeting key pathways of cancer signaling and differentiation is defining a new era in the treatment of advanced ovarian cancer. More phase III studies are, however, needed to further evaluate the efficacy and toxicity of these new agents. Importantly, the identification of certain predictive biomarkers may optimize treatment’s efficacy distinguishing the target group that would derive the most benefit through this patient-tailored approach.
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