

New Strategies in the Treatment of Ovarian Cancer: Current Clinical Perspectives and Future Potential

Susana Banerjee and Stanley B. Kaye

Abstract

The treatment of ovarian cancer is set to undergo rapid changes, as strategies incorporating molecular targeted therapies begin to take shape. These are based on a better appreciation of approaches targeting the tumor microenvironment as well as specific subtypes of the disease, with distinct molecular aberrations. Targeting the VEGF pathway through bevacizumab is clearly effective, with positive randomized trials at all disease stages; targeting defective homologous recombination repair pathways with PARP inhibitors is also proving successful in a substantial proportion of patients with high-grade serous ovarian cancer. In this article, we will review progress in these two leading areas and also discuss the potential for targeting other pathways and receptors that may be activated in ovarian cancer, including the RAS/RAF/MEK and PI3K/AKT/mTOR pathways, the ErbB and IGF family of receptors, mitotic check points, and also the folate receptor. Here, single-agent therapy may play a role in selected cases but essential components of future strategies should include combination treatments aimed at dealing with the key problem of drug resistance, together with rational approaches to patient selection. *Clin Cancer Res*; 19(5); 961–8. ©2013 AACR.

Background

Ovarian cancer is estimated to be diagnosed in more than 225,000 women per year worldwide and remains a significant cause of gynecological cancer mortality (~140,000 deaths/y; ref. 1). Unfortunately, the majority of women continue to present at advanced stages and the overall 5-year survival rate is around 40%. The current standard of care for newly diagnosed ovarian cancer is a combination of optimal cytoreductive surgery and platinum-based chemotherapy. Key advances in radical surgery and chemotherapy strategies have led to improved, albeit modest, clinical outcomes. Despite advances, there remains a significant risk of recurrence and resistance to therapy and when this occurs, ovarian cancer is currently incurable. Hence, there is an urgent need to develop smarter treatment options.

Epithelial ovarian cancer (EOC) is recognized as a heterogeneous disease and is divided according to histologic subtypes: high-grade serous, low-grade serous, clear cell, endometrioid, and mucinous (2). Each histologic subtype is associated with a distinct clinical behavior (response to

chemotherapy, pattern of metastases, survival) but has historically been treated as one entity. The identification of distinct molecular pathways characteristic of individual subtypes (3) has fuelled enthusiasm for the development of targeted therapies (4) directed at specific subtypes of ovarian cancer (Fig. 1).

Molecularly targeted agents hold the promise of greater selectivity with lower toxicity than conventional chemotherapy. Over the last few years, there have been several landmark reports in EOC giving rise to the development of molecular-driven, patient-selective clinical trials and changes in clinical practice.

On the Horizon

Angiogenesis inhibitors

VEGF is a key mediator of angiogenesis, a process that is important in ovarian cancer growth and metastasis. Phase III clinical trials of bevacizumab, a monoclonal antibody against VEGF-A, have shown significant clinical activity in EOC. Two first-line studies, GOG-0218 (5) and ICON7 (6), addressed the addition of bevacizumab to the carboplatin and paclitaxel combination followed by maintenance therapy for a defined period. In both phase III trials, significant improvements in the primary endpoint, progression-free survival (PFS), were attained through the use of concurrent and maintenance bevacizumab despite key differences in trial design (GOG-0218: HR, 0.72; $P < 0.001$; ICON7: HR, 0.81; $P < 0.004$). Furthermore, in ICON7, an overall survival (OS) advantage of almost 8 months [28.8 vs. 36.6 months; HR, 0.64; 95% confidence

Authors' Affiliation: Gynaecology Unit, The Royal Marsden NHS Foundation Trust, London, United Kingdom

Corresponding Author: Stanley B. Kaye, Division of Clinical Studies, Institute of Cancer Research, and the Drug Development Unit, Royal Marsden NHS Trust, The Royal Marsden NHS Foundation Trust, Sycamore House, Downs Road, Sutton, Surrey, SM2 5PT, United Kingdom. Phone: 4420-8661-3539; Fax: 4420-8661-3541; E-mail: stan.kaye@rmh.nhs.uk

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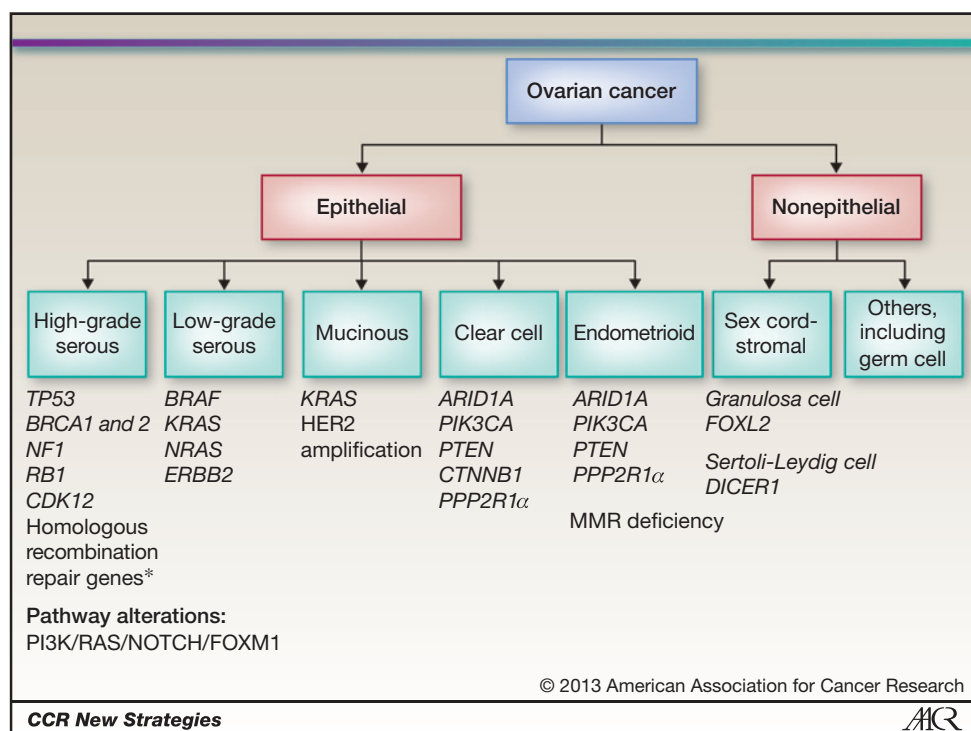


Figure 1. Histologic subtypes of epithelial ovarian carcinoma and associated mutations/molecular aberrations. *, *CHK2*, *BARD1*, *BRIP1*, *PALB2*, *RAD50*, *RAD51C*, *ATM*, *ATR*, *EMSY*, Fanconi anemia genes. MMR, mismatch repair. References 22, 34, 44, 58–65.

interval (CI), 0.48–0.85, $P < 0.002$] was reported in the bevacizumab arm for the subgroup of patients with a poor prognosis (high-risk group defined as FIGO stage IV disease or FIGO stage III disease and more than 1.0 cm of residual disease after debulking surgery; ref. 6). Although the mature OS results for GOG-0218 and ICON7 are awaited, on the basis of the above results, the European Medicines Agency approved the use of bevacizumab in combination with carboplatin and paclitaxel as first-line therapy.

The next question was whether bevacizumab has a role in relapsed ovarian cancer. The OCEANS study (7), a phase III trial of bevacizumab in combination with chemotherapy (carboplatin with gemcitabine) followed by maintenance therapy until progression in first-line platinum-sensitive (recurrence >6 months after front-line platinum-based therapy) relapse, also reported a significant improvement in the primary endpoint, PFS, with the addition of bevacizumab (8.4 vs. 12.4 months; HR, 0.48; $P < 0.0001$). For patients with platinum-resistant disease, an impressive, statistically significant improvement in PFS (3.4 vs. 6.7 months; HR, 0.48; $P < 0.001$) was shown in the AURELIA study (8), a phase III trial of bevacizumab in combination with chemotherapy (PEGylated liposomal doxorubicin, topotecan, or weekly paclitaxel) until progression. This is the first phase III study in platinum-resistant ovarian cancer to have shown benefit with a targeted therapy. Despite the lack of final OS results, the findings from both OCEANS and AURELIA strongly support a role for bevacizumab in recurrent disease, and the European Medicines Agency have given a favorable opinion for approval in first-line

platinum-sensitive relapse. However, in the United States at this stage, approval has not yet been sought for the use of bevacizumab in ovarian cancer, and debate continues about the most appropriate use of this agent in this disease.

Other agents that directly inhibit VEGF include aflibercept, a VEGF-ligand-binding fusion protein that acts as a decoy receptor for the binding of VEGF. This approach in combination with chemotherapy appears to have substantial clinical efficacy (overall response rate 54% in combination with docetaxel), although the advantages over bevacizumab are unclear (9).

The main limitations of bevacizumab, apart from cost, are toxicities (e.g., bowel perforation, hypertension) and resistance to treatment. The key challenges to address next, therefore, include (i) how to select which patients will derive most benefit and at which point during the treatment pathway (i.e., upfront, platinum-sensitive or platinum-resistant setting) and (ii) how to overcome resistance to bevacizumab? At present, there are no validated biomarkers predicting clinical efficacy following bevacizumab in ovarian cancer although studies investigating gene expression arrays and isoform-specific plasma VEGF-A measurements are ongoing. Advances in imaging techniques, for example, multiparametric MRI, fluorodeoxyglucose positron emission tomography (10, 11) appear promising and prospective clinical trials including imaging-based endpoints are planned. Resistance mechanisms include the upregulation of alternative proangiogenic signaling pathways [fibroblast growth factor (FGF), platelet-derived growth factor receptor (PDGFR), c-Met] and

have raised the question of whether targeting additional pathways will be a successful strategy. Several tyrosine kinase inhibitors (TKI) that target VEGF receptors also inhibit other proangiogenic molecules (for example, FGF: nintedanib, brivanib, dovitinib; PDGFR: cediranib, pazopanib; c-Met: cabozantinib) and are under investigation in various trials in ovarian cancer. These include randomized trials (first- or second-line) involving nintedanib, pazopanib, and cediranib, and in addition the VEGFR TKI sunitinib is under evaluation in clear cell ovarian cancer, which is often resistant to conventional therapy.

Trebananib (AMG386) is a peptide-Fc fusion protein that prevents interactions between angiopoietin-1 and angiopoietin-2 expressed on vascular endothelial cells with the Tie2 receptor, thereby inhibiting vascular maturation and reducing the impact of VEGF stimulation. In clinical trials so far, trebananib is administered weekly in combination with chemotherapy and as maintenance therapy. Efficacy seems to be dose dependent and the toxicity profile appears to differ from bevacizumab: Peripheral edema, presumably due to disruption of the angiopoietin axis, is common, whereas hypertension and proteinuria are not seen (12). Important questions are (i) based on efficacy and a more tolerable toxicity profile, could trebananib replace bevacizumab and (ii) can targeting the angiopoietin axis address resistance to bevacizumab in patients progressing on this treatment? The ongoing first-line (TRINOVA-3) and recurrent (TRINOVA-1 and 2) ovarian cancer clinical trials will help answer the above.

As an increasing number of patients will have received bevacizumab, it will be increasingly important to identify rational treatment options in patients who progress on bevacizumab. In a randomized phase II discontinuation study of brivanib (targets VEGFR and FGFR), which included patients who had received antiangiogenic agents, clinical efficacy was seen in patients previously treated with VEGF inhibitors (mainly bevacizumab: 17% partial response; 30% disease stabilization and may relate to FGF inhibition; ref. 13). Data on other antiangiogenic agents in this patient population will be important to ascertain. Options to potentially overcome resistance include combination approaches—either "vertical," for example, bevacizumab plus VEGFR inhibitor sorafenib/sunitinib or "horizontal," for example, bevacizumab and either a vascular disrupting agent or angiopoietin antagonist, AMG386. The increased toxicity potentially associated with combination strategies needs to be carefully considered (14) and a sequential approach with an alternative single agent antiangiogenic after bevacizumab may be an alternative strategy. In addition, the role for repeating or continuing bevacizumab at progression and substituting an alternative chemotherapy is being explored.

There are a number of other antiangiogenic targets that have emerged that are becoming more clinically relevant and include Zeste homolog 2 (EZH2) and the Notch/Delta-like ligand 4 (Dll4). EZH2 has been linked to increased angiogenesis through methylation and

silencing of the anti-angiogenic factor vasohibin 1. Pre-clinical studies have shown that silencing of EZH2 using siRNA inhibits angiogenesis and ovarian cancer growth (15). Dll4 has been associated with poor outcome following anti-VEGF therapy and RNA interference-mediated silencing of Dll4 has been shown to reduce angiogenesis and tumor growth in ovarian cancer models (16). This approach appears promising and a phase I clinical trial of REGN 421, a monoclonal antibody against Dll4, is underway.

In addition, a mechanistic link has recently been made between thrombocytosis and poor survival in ovarian cancer, which may be relevant to antiangiogenesis. This appears to involve tumor-derived IL6 stimulation of hepatic thrombopoietin with a consequent increase in PDGF particularly affecting pericytes (17). Mouse models have shown that antiplatelet antibody significantly reduced tumor angiogenesis and growth. This approach needs further exploration in clinical trials.

PARP inhibitors

PARP inhibitors exploit the concept of "synthetic lethality"—targeting one of the genes in a synthetic lethal pair in which the other is defective (e.g., *BRCA* mutation) selectively kills tumor cells while sparing normal cells (thereby limiting toxicity), potentially creating a substantial therapeutic window (18). Patients harboring mutations in *BRCA1/2* were predicted to be highly susceptible to treatment with PARP inhibitors (19, 20) and this proof-of-concept was supported in a phase II study of olaparib in patients with germ-line *BRCA1* or *BRCA2* mutations with recurrent ovarian cancer [33% Response Evaluation Criteria in Solid Tumors (RECIST) response rate at 400 mg twice daily] which included patients with platinum-resistant disease (21). A wider use of this approach was envisaged in view of the fact that up to 50% of high-grade serous, sporadic ovarian cancers have defective homologous recombination repair pathways (including *BRCA* methylation and somatic *BRCA* mutations) which may confer sensitivity to PARP inhibition (22). Efficacy was indeed confirmed in a phase II study of olaparib in this patient population, although responders were mainly seen in those with platinum-sensitive disease with a response rate of 50% (23). This was further explored in a double-blind, placebo-controlled randomized phase II study in which patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer (who had achieved a response following their most recent platinum-based regimen) were randomized to either olaparib or placebo maintenance therapy (24). About 22% of patients were known to have a *BRCA* mutation and 64% had unknown *BRCA* status. PFS (according to RECIST criteria) was significantly prolonged with olaparib compared with the placebo arm (median, 8.4 vs. 4.8 months; HR, 0.35; $P < 0.001$), although an initial analysis indicated that this does not translate into an overall survival benefit. The possibility exists that although PARP inhibitors may delay disease progression,

treatment could subsequently impact response to further chemotherapy. However, an analysis of post-olaparib chemotherapy in patients with germ-line *BRCA* mutations indicates that sensitivity, at least in this population, appears to be maintained (25). The impact of PARP inhibitors may differ according to the *BRCA* mutation status and preliminary analysis suggests that the benefit of olaparib maintenance therapy, at least in terms of PFS, was larger in known *BRCA* germ-line mutation carriers (PFS: HR, 0.10).

The key issues for the development of PARP inhibitors are patient selection and single versus combination strategies. There is little doubt that PARP inhibitors should be further developed toward registration in *BRCA* mutation-associated ovarian cancer (26), and a maintenance treatment approach is particularly promising. For patients with *BRCA*-associated platinum-resistant disease, a registration strategy for PARP inhibitors incorporating randomized controlled trials is less straight forward as it is becoming clear that higher response rates may be seen with certain chemotherapy agents such as liposomal doxorubicin in *BRCA* mutation carriers (27). Combination approaches with chemotherapy, based on the hypothesis of a chemosensitization effect, are being tested. However, a limitation is the increased myelosuppression seen with these regimens so far and the optimal duration of PARP inhibition with chemotherapy is not yet defined. In a randomized phase II study of olaparib with carboplatin and paclitaxel, the response rate was not increased compared with chemotherapy alone (28). However, in keeping with the maintenance therapy trial previously reported (24), the PFS was significantly longer in the olaparib arm which is likely to be due to the maintenance treatment rather than the combination effect with chemotherapy.

Other combination strategies of interest are PARP inhibitors with phosphoinositide 3-kinase (PI3K) inhibitors or antiangiogenic agents. Preclinical models of breast cancer have identified that in the context of an upregulated PI3K pathway, PI3K inhibition is associated with the loss of homologous recombination repair capability resulting in sensitization to PARP inhibitors (29, 30). The rationale for the PARP inhibitor/antiangiogenic combination is based on observations (i) that PARP inhibitors may lead to increased VEGFR2 phosphorylation and subsequent activation of endothelial cell survival, an effect which has been shown to be reversed by a VEGFR2 inhibitor (31), and (ii) that VEGFR2 inhibition leads to hypoxia, which can lead to acquisition of HR defects and sensitivity to PARP inhibitors in hypoxic cancer cells (32). In addition to olaparib, other PARP inhibitors under investigation in this disease include rucaparib, veliparib, niraparib, and BMN-673.

Ras/Raf/MEK/ERK pathway

Low-grade serous ovarian carcinoma (LGSOC), a rare subtype of EOC, has a distinct clinical behavior char-

acterized by younger age at presentation, more indolent growth pattern, and poor responses to systemic therapy (33). Activation of the mitogen-activated protein kinase (MAPK) signaling pathway may be very important as *BRAF* and *KRAS* mutations were initially reported in up to 68% of cases (33% *BRAF*, 35% *KRAS*- mutually exclusive; ref. 34). Although the incidence of *BRAF* mutations appears lower in recent reports (35), the Ras/MEK/ERK pathway is still an attractive therapeutic target in this notoriously difficult disease. A phase II trial of the MEK1/2 inhibitor selumetinib (AZD6244) in 52 patients with recurrent LGSOC has shown promising results (36): The overall response rate was 15.4%, disease stabilization 65%, and median PFS 11 months. In this study, 6% *BRAF*, 41% *KRAS*, and 15% *NRAS* mutations were identified and response was not correlated with mutational status. Phase II trials of other MEK inhibitors such as GSK1120212 (Trametinib) are planned, and combination strategies of MEK and AKT inhibitors (currently in phase I trials) are also under consideration.

In primary mucinous ovarian cancer, which is frequently resistant to conventional chemotherapy, the Ras/Raf pathway is also an appropriate therapeutic target.

Overcoming Platinum and Taxane Resistance

PI3K/AKT/mTOR pathway

Activation of the PI3K pathway through mutations of *PIK3CA*, *AKT*, or inactivating mutations of *PTEN* is rare in the high-grade serous subtype (<5%), although may be seen in up to 30% of clear cell and endometrioid ovarian carcinomas. However, it is unclear whether an aberration in this pathway in an individual's tumor is the critical driver of cancer growth and therefore susceptible to targeted inhibition in ovarian cancer. Several agents are being explored in clinical trials of ovarian cancer and it will be important to correlate any evidence of clinical activity with pathway alterations. Probably of wider clinical applicability are preclinical studies that have suggested a potential for modulation of this pathway to overcome resistance to chemotherapy in ovarian cancer (37). Clinical trials of chemotherapy in combination with either AKT or TORC1/2 inhibitors are planned.

ErbB family

Although increased expression of EGF receptor (EGFR) is common in ovarian cancer (up to 60%), mutations are rare (<4%; ref. 38) and clinical trial results with single-agent EGFR inhibitors (erlotinib, gefitinib) are disappointing (39, 40). Similarly, HER2-targeted therapy (trastuzumab, pertuzumab) has proven to be of no benefit in unselected cases (41–43), although it has been proposed that HER2 activation as measured by phosphorylation of HER2 may be more predictive of sensitivity to HER2-targeted agents (42). HER2 overexpression or amplification has been described in up to 18% of advanced

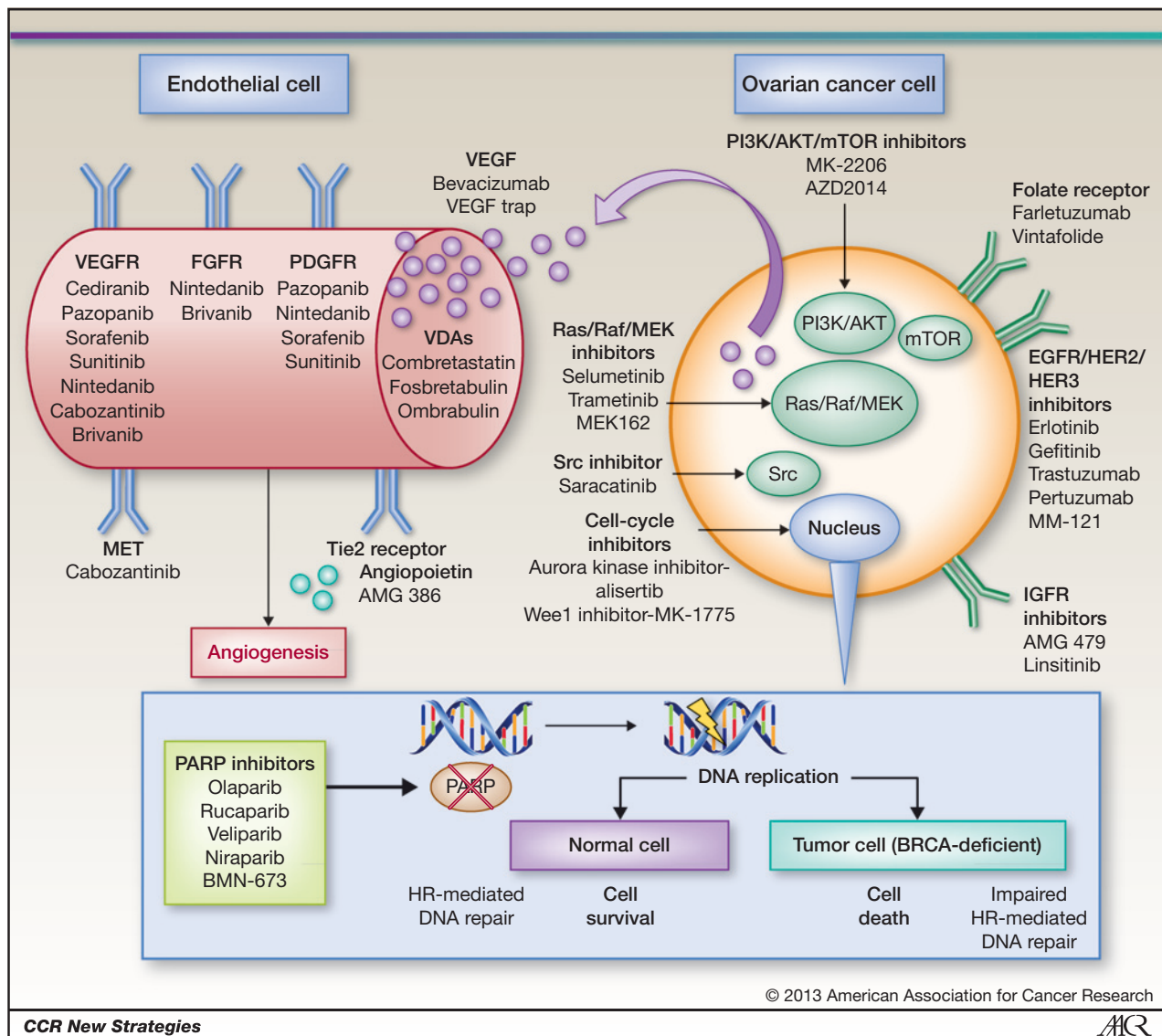


Figure 2. Targeted therapies in ovarian cancer.

mucinous carcinomas, and HER2-directed treatment approaches for this subgroup of patients should be considered (44). However, targeting ErbB3 (HER3) may be more promising for a larger group of patients. ErbB3 (HER3) forms a heterodimer with ErbB2 (HER2) and stimulates cell survival pathways through activation of MAPK and AKT pathways. HER3 has been associated with poor prognosis (45) and resistance to chemotherapy including taxanes (46). An autocrine NRG1-driven/activated ErbB3 loop promoting ovarian cancer cell proliferation has been described and disruption of this circuit with a monoclonal ErbB3-directed antibody (MM-121) significantly inhibited tumor growth in mouse xenograft models (47). MM-121 is currently under investigation in phase II trials combined with paclitaxel in ovarian cancer.

Other

Multiple other signaling molecules are also implicated in overcoming resistance to chemotherapy and targeted agents in ovarian cancer, including the insulin-like growth factor (IGF) receptor and Src. A phase II study of the Src inhibitor dasatinib in relapsed ovarian cancer was disappointing, with no objective response reported (48). In addition, saracatinib (Src inhibitor) in combination with carboplatin and paclitaxel failed to show benefit in platinum-sensitive disease (49). However, preclinical studies suggest that Src inhibition has the potential to reverse paclitaxel resistance and merits further exploration in ovarian cancer (50). The IGF pathway has also been shown to modulate paclitaxel resistance (51). Saracatinib (Src inhibitor) and OSI-906 (linsitinib; a small-molecule dual kinase inhibitor of both IGF-1

receptor and insulin receptor) have entered phase II clinical trials in combination with weekly paclitaxel in platinum-resistant ovarian cancer. Furthermore, overexpression of IGF-1 and growth inhibition with OSI-906 was reported in preclinical models of LGSOC (52) and, therefore, in addition to MEK inhibition, targeting the IGF pathway may be another potential therapeutic approach in this setting.

Another potential target is Wee-1 kinase which regulates the G₂-M checkpoint. Inhibition of Wee-1 kinase may lead to chemosensitization of p53-deficient tumor cells (53), which are characteristic of high-grade serous ovarian cancer. On the basis of the encouraging activity seen in phase I clinical trials of MK-1775 (54), a selective inhibitor of Wee-1 kinase, a randomized trial in platinum-sensitive relapsed disease is underway. Other mitotic checkpoint inhibitors include the selective aurora kinase A inhibitor MLN8237 (alisertib) and, although it has limited single-agent clinical activity in platinum-resistant ovarian cancer (55), randomized trials in combination with paclitaxel are ongoing.

The folate receptor is overexpressed in more than 90% of ovarian cancers, and several anti-folate receptor strategies are under investigation, including farletuzumab (MORab-003, Morphotek Inc.), a monoclonal antibody directed against the α -folate receptor. EC145, a conjugate of a vinblastine analogue to folate, appears promising. An interim analysis of a randomized, phase II study of EC145 + liposomal doxorubicin reported a greater than 2-fold increase in median PFS with the addition of EC145 (24 vs. 11.7 weeks, HR, 0.50; *P* = 0.014) in platinum-resistant ovarian cancer, and clinical benefit was most clearly seen in the subgroup of patients with high folate receptor activity as assessed on whole-body SPECT scanning using Tc-labeled folate (56).

Drug resistance has generally been considered to be characteristic of so-called "stem cells," although these have proved difficult to isolate and characterize. However, a study on ascites in patients with relapsed disease identified EZH2 as playing a key role in the maintenance of a drug-resistant stem cell-like subpopulation of tumor cells (57) and this is an area of new drug development.

At present, key mutations identified in genes such as *ARID1A* (in clear cell and endometrioid subtype; ref. 58)

and *TP53* (in high-grade serous subtype; ref. 22) are not directly "druggable." However, advances in high-throughput technologies are providing the opportunity for genomic-based drug discovery studies that may lead to the identification of new agents in the treatment of ovarian cancer.

Conclusions

Understanding more about how best to use our increasing knowledge of the molecular abnormalities involved in ovarian cancer will be critical in improving clinical outcome in ovarian cancer. Of the many targeted therapies currently under evaluation in phase I/II and III studies (Fig. 2), the most promising strategies developed so far are the anti-angiogenic agents and PARP inhibitors. Challenges facing the success of targeted therapy include the identification of the correct population to treat, as well as a better appreciation of mechanisms underlying drug resistance. It is generally accepted that tumor biopsies taken at the time of progression are likely to yield important information for molecular profiling to direct targeted agents. However, the recognition of inter- and intratumor heterogeneity poses a further challenge in terms of how best to interpret these results in the clinic. To complement biopsy data, information from other sources such as circulating tumor DNA, taken together with novel approaches to molecular imaging, should form part of a comprehensive approach to predictive biomarker validation in clinical trials of ovarian cancer.

Disclosure of Potential Conflicts of Interest

S. Kaye is on the advisory board of and has honoraria from speakers bureau from Roche, AstraZeneca, Clovis, Array, Sanofi-Aventis, and Astellas. S. Banerjee is on the advisory board of Tesaro and Array.

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