

New Strategies in Ovarian Cancer: Translating the Molecular Complexity of Ovarian Cancer into Treatment Advances

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Abstract

An improved understanding of the genomics of ovarian cancer and the separation of ovarian cancer into histologically and molecularly defined subgroups have affected drug development and clinical trial design in ovarian cancer. Active therapies that have been tested in ovarian cancer include agents that inhibit angiogenesis and poly (ADP-ribose) polymerase inhibitors (PARPi). However, no FDA drug approvals for ovarian cancer have been granted since 2006, and overall survival improvements have been difficult to achieve with new agents. The genomic complexity of ovarian cancer and modest single-agent activity of many biologic agents in this disease have led to testing of biologic agent combinations. In this article, we review recent advances in the understanding of the molecular diversity of ovarian cancer as well as emerging therapeutic strategies such as new agents and biologic combinations that attempt to target multiple aberrant pathways in this cancer. *Clin Cancer Res*; 20(20); 5150–6. ©2014 AACR.

Disclosure of Potential Conflicts of Interest

U.A. Matulonis is a consultant/advisory board member for AstraZeneca (uncompensated), Clovis, Merck, and Tesaro. No potential conflicts of interest were disclosed by the other author.

CME Staff Planners' Disclosures

The members of the planning committee have no real or apparent conflict of interest to disclose.

Learning Objectives

Ovarian cancer is a molecularly complex malignancy that is now divided into subtypes that are distinguished histologically and genomically. Upon completion of this activity, the participant should have a better understanding of the advances in the genomics of ovarian cancer, the classification of ovarian cancer subtypes, and the emerging therapeutic strategies in clinical trials.

Acknowledgment of Financial or Other Support

This activity does not receive commercial support.

Background

Ovarian cancer is a deadly disease that affects women globally, is diagnosed at an advanced stage in most patients, and has no effective screening tests for early detection (1–4). The worldwide incidence of this cancer is 225,500 diagnoses per year; in the United States in 2014, 21,980 women will be diagnosed with ovarian cancer (1, 2). Global mortality of this cancer remains high, with 140,200 deaths per year, and minimal improvement in mortality has been observed over the past decade (5). Most patients will recur after being diagnosed with advanced ovarian cancer; for patients with platinum-sensitive recurrence (defined as cancer recurring

≥6 months after the last platinum), additional platinum-based therapy is given (6). For patients with recurrent platinum-resistant cancer (defined as cancer recurring <6 months after last platinum), single-agent chemotherapy is administered (6). The specific criteria by which platinum sensitivity is defined [e.g., via Response Evaluation Criteria in Solid Tumors (RECIST) or Gynecologic Cancer InterGroup (GCIG) CA125] can vary between trials and in the published literature, and the lack of uniform definition should be taken into consideration when interpreting trial results.

Treatment strategies that have led to an overall survival (OS) improvement for newly diagnosed patients have included the addition of paclitaxel to platinum, the use of intraperitoneal cisplatin in patients with optimally cytoreduced cancer (<1 cm of residual cancer after upfront cytoreductive surgery), and incorporation of weekly paclitaxel instead of every-3-week paclitaxel as part of upfront treatment for ovarian cancer (7–9). Neoadjuvant chemotherapy has emerged as a treatment alternative, especially in patients who are too ill or frail or whose cancer is too extensive to

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doi: 10.1158/1078-0432.CCR-14-1312

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undergo upfront cytoreductive surgery (10, 11). Although trials of various biologic agents, most commonly antiangiogenics, have demonstrated progression-free survival (PFS) benefit in randomized trials, no trials have demonstrated an improvement in OS until recently when the addition of cediranib to platinum-based chemotherapy in patients with platinum-sensitive recurrent ovarian cancer resulted in an OS benefit (12–17).

Nevertheless, the realization that ovarian cancer is composed of several different subtypes with different molecular landscapes, improved understanding of the genomics of these subtypes, and the development of new active biologic agents all have the promise of improving ovarian cancer outcomes and mortality (4, 18). In addition, the shift in trial design toward eligibility restriction to specific histologic subtypes rather than testing agents in an unselected population provides potential opportunity for improved therapy in targeted populations.

On the Horizon

A challenge for improved treatment strategies for ovarian cancer is to develop new agents that are not only active against ovarian cancer but are also approvable by regulatory agencies such as the FDA and the European Medicines Agency (EMA). Achievement of OS improvement in ovarian cancer, a frequent standard for regulatory approval, has proven challenging despite improvements in PFS. Reasons for the difficulty in demonstrating OS improvement are not fully understood; possible reasons include the availability of many treatment options following progression, the lack of stratification of histologic subtypes in previous trial designs, thus diluting the effectiveness of agents that might have shown benefit when tested in molecularly or genomically defined subgroups, and the fact that some patients in randomized trials will eventually cross over to the other treatment, thus possibly affecting OS. For example, in a phase II maintenance study of the poly (ADP-ribose) polymerase inhibitor (PARPi) olaparib in patients with recurrent platinum-sensitive high-grade serous ovarian cancer (HGSC), 23% of patients in the control arm ultimately received a PARPi off study, and an OS benefit was not observed even in the setting of a marked PFS improvement (19, 20). Because of the difficulties in attaining OS benefits and hence the lack of drug approvals in the United States for ovarian cancer, achievement of significant PFS benefit as a reason for drug approval has been endorsed (21, 22), and this has been a mechanism for drug approval in cancers other than ovarian cancer (23, 24). In addition, trials that demonstrate a PFS benefit but no OS improvement must define a clinically and statistically meaningful PFS improvement, document patient benefit using patient-reported outcomes and quality-of-life measures, and demonstrate acceptable acute and long-term toxicities.

Molecular classification of ovarian cancer

The recognition that ovarian cancer is not one cancer and instead is composed of several subtypes that are histolog-

ically and molecularly unique has begun to affect treatment strategies (4, 11, 25, 26). These histologic subtypes include serous, endometrioid, clear cell, and mucinous subtypes. Within subtypes, low and high grades can additionally exist, especially for serous and endometrioid types.

HGSC is the most common ovarian cancer subtype, and the genomics of this subtype have been the most studied to date (27–30). The Cancer Genome Atlas (TCGA) project and others have analyzed HGSC that has revealed frequent somatic copy number alterations, defective homologous recombination (HR) in approximately 50% of analyzed cancers because of germline and somatic *BRCA* mutations, epigenetic inactivation of *BRCA*, and abnormalities of other DNA repair genes, as well as defective NOTCH, PI3K, RAS/MEK, and FOXM1 pathway signaling (27). The most commonly mutated gene in HGSC is *TP53* (27), but to date this has not been a druggable target. In HGSC, germline *BRCA1/2* (*gBRCA*) mutations have been identified in up to 17% of unselected patients (31), and as a result, treatment guidelines have endorsed germline genetic testing for all patients with ovarian, fallopian tube, or peritoneal cancer (32). Within HGSC, emerging data have revealed further subdivision based on gene expression (27, 33); the TCGA has identified four subtypes based on gene expression and content: differentiated, immunoreactive, mesenchymal, and proliferative, with differences in outcome existing between these groups (33). For example, recent results from two groups retrospectively analyzing gene expression data from ovarian cancer samples from ICON7, an upfront study of bevacizumab in newly diagnosed ovarian cancer (13), demonstrated outcome differences between arms based on expression data (34, 35); however, because these studies defined their subtypes using different algorithms, comparing the results of these studies is challenging. Moving forward, general agreement on how molecular subgroups are defined will allow more widespread use of expression data in future clinical trial design as a possible means to predict prognosis as well as treatment benefit.

An additional consideration of the genomic complexity of HGSC is the molecular diversity that occurs within tumor sites of an individual patient. Bashashati and colleagues (36) examined 31 spatially and temporally separated specimens from 6 patients with HGSC and found widespread intratumor genomic variability even within tumors from the same patient. Thus, isolated tissue biopsies obtained at recurrence may vastly underestimate the genomic landscape, and other technologies such as circulating DNA and single-cell genotyping may provide additional insight into mechanisms of disease recurrence and resistance. This level of molecular diversity at the time of diagnosis, the paucity of druggable driver mutations, and the presence of high copy number alterations in multiple signaling pathway genes characterize the genomic complexity of HGSC and may influence response rates and PFS, in addition to providing insight into why OS benefits have been so difficult to achieve in ovarian cancer.

Other histologic subtypes of ovarian cancer also have potentially therapeutically exploitable genetic abnormalities,

such as low-grade serous cancer (LGSC), clear cell ovarian cancer, and mucinous cancers, and several recent reviews have described these abnormalities in detail (4, 18, 26, 37–39). For example, LGSC has increased frequency of *BRAF* and *RAS* mutations, and the MEK inhibitor selumetinib has demonstrated activity in LGSC (40). Mucinous cancers that display platinum insensitivity can have *RAS* mutations (37), and mutations in *ARID1A*, *PIK3CA*, *PTEN*, and *CTNNB1* as well as genomic complexity are seen in clear cell cancers (4, 18, 39). Of note, somatic mutations in HR genes are not isolated to HGSC alone, and germline or somatic mutations in HR genes have been found in approximately one third of nonserous as well as HGSC histologies (41).

New treatment strategies

Antiangiogenesis agents. Bevacizumab is the most studied antiangiogenic agent in ovarian cancer; in trials in the upfront as well as recurrent platinum-sensitive and platinum-resistant settings, addition of bevacizumab has resulted in PFS improvement, but no OS improvement (12–15). Currently, other antiangiogenic agents, such as nintedanib [vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI)] and trebananib (peptide-Fc fusion protein that inhibits binding of angiotensin 1 and 2 to the Tie2 receptor), are being tested in the upfront and recurrent settings (16, 42). Results of a phase III placebo-controlled study that tested carboplatin/paclitaxel ± nintedanib showed improved median PFS for the nintedanib arm versus placebo [17.3 vs. 16.6 months; hazard ratio, 0.84; 95% confidence interval (CI), 0.72–0.98; $P =$

0.0239]; data for OS are not mature (42). Many other trials in the upfront setting are currently awaiting mature results and are testing questions regarding dose and length of duration of antiangiogenics.

Studies of antiangiogenic agents in recurrent ovarian cancer have not demonstrated OS benefits until just recently. In ICON6, combining the oral VEGFR TKI cediranib (43) with platinum-based chemotherapy in platinum-sensitive recurrent ovarian cancer followed by cediranib maintenance improved OS in a preliminary analysis (17). PFS improved from 9.4 months with chemotherapy alone to 12.6 months for the cediranib/chemotherapy arm, while OS increased from 17.6 to 20.3 months with the cediranib/chemotherapy combination (hazard ratio, 0.70; $P = 0.0419$; ref. 17). These results represent the first time a biologic therapy combined with standard-of-care chemotherapy has resulted in an OS benefit in ovarian cancer.

PARP inhibitors. PARPis are a unique class of agent that interferes with repair of DNA single-stranded breaks (44). These agents have shown single-agent activity in recurrent ovarian cancer of up to 30%, with the highest anticancer activity demonstrated in *gBRCA* ovarian cancer and in platinum-sensitive disease (45, 46). Table 1 lists the current oral PARPis in clinical trials for ovarian cancer and the status of ongoing studies. A randomized double-blind placebo-controlled phase II study of olaparib maintenance following response to at least a second platinum-based regimen in recurrent platinum-sensitive HGSC demonstrated statistically significant improvement in median PFS from 4.8 months on placebo to 8.4 months on olaparib (hazard ratio, 0.35; $P < 0.001$) without OS benefit (19); randomization to

Table 1. PARP inhibitors in clinical trials for ovarian cancer and examples of ongoing trials

PARP inhibitor	Reference(s)	Route	Examples of studies for ovarian cancer that are ongoing or completed
Olaparib (AZD2281)	(19, 20, 45, 46, 51–53, 56)	Oral	Phase I: Combinations ongoing Phase II: Based on study 19 results, EMA application filed; ODAC "no" vote in June 2014 for accelerated approval Phase III: SOLO 1: newly diagnosed <i>gBRCA</i> ovarian cancer used as maintenance following platinum-based chemotherapy in <i>gBRCA</i> mutation carriers; SOLO 2: platinum-sensitive recurrence as maintenance following platinum-based chemotherapy in <i>gBRCA</i> mutation carriers
Veliparib (ABT-888)	(50)	Oral	Phase I: Single-agent and combination studies Phase II: <i>gBRCA</i> recurrent ovarian cancer, combination studies with chemotherapy
Rucaparib (CO338, AGO14699, and PF01367338)	(48)	Oral	Phase I: Single agent completed Phase II: ARIEL2 ongoing Phase III: ARIEL3 ongoing in maintenance in platinum-sensitive recurrent ovary cancer
Niraparib (MK-4827)	(49)	Oral	Phase I: Single agent completed Phase III: NOVA trial ongoing in maintenance in platinum-sensitive recurrent ovary cancer
BMN673	(44)	Oral	Phase I and dose expansions in <i>gBRCA</i> ovarian cancer

Abbreviation: ODAC, Oncology Drugs Advisory Committee.
Adapted with permission from Liu et al. (44).

either olaparib or placebo occurred following the most recent platinum-based regimen, and eligibility mandated that patients have an objective RECIST or CA125 response to this last platinum (19). Women with *gBRCA* mutation demonstrated an even more pronounced PFS benefit (11.2 vs. 4.3 months; hazard ratio, 0.18; $P < 0.0001$) in favor of olaparib maintenance (20). On the basis of these results, olaparib was filed with the FDA for accelerated approval as well as with the EMA; however, the Oncologic Drugs Advisory Committee of the FDA voted against accelerated approval for olaparib as maintenance therapy in *gBRCA* mutation carriers, favoring waiting for the results of the phase III SOLO2 study (47). SOLO2, which is currently enrolling patients, was designed similarly to the prior phase II trial, but is restricted to patients with *gBRCA* mutations and HGSC or high-grade endometrioid histology. In a parallel phase III study in the upfront setting (SOLO1), olaparib is being tested as maintenance therapy following initial treatment in *gBRCA*-mutated ovarian cancer. Other PARPis, such as niraparib and rucaparib, are in phase III studies as maintenance therapy for platinum-sensitive recurrent ovarian cancer after response to platinum-based chemotherapy (48, 49); veliparib has been testing in phase II trials (44, 50). PARPis have also been combined with chemotherapy with evidence of anticancer activity (51, 52; and a review of this topic is found in ref. 44). However, because of the myelosuppression observed with PARPi and chemotherapy combinations, which can be multilineage, full doses of both agents are often not achievable, raising concerns of whether combinations of PARPis and chemotherapy could result in attenuated anticancer activity.

Combination strategies. Combinations of biologics that target various pathways and exhibit preclinical synergy may represent a new treatment paradigm for HGSC given its genomic complexity. Recently, provocative results from a phase II study of the combination of olaparib and cediranib were reported in patients with platinum-sensitive recurrent ovarian cancer (53). Ninety patients were randomized to either olaparib alone versus the combination of cediranib/olaparib; median PFS was significantly longer with cediranib/olaparib compared with olaparib alone (17.7 vs. 9 months; hazard ratio, 0.42; $P = 0.005$; ref. 53). Subset analysis by *gBRCA* mutation status revealed a significant improvement in PFS in *gBRCA* wild-type or unknown patients receiving cediranib/olaparib compared with olaparib alone (16.5 vs. 5.7 months; $P = 0.008$) with no significant improvement in PFS observed in the *gBRCA* patients (19.4 vs. 16.5 months; $P = 0.16$; ref. 53). These results raise the possibility that combining targeted therapies may result in greater clinical effect, and further studies with the cediranib/olaparib combination are under development.

Other novel combinations in clinical testing include PARPis and PI3K inhibitors; preclinical results combining olaparib and the PI3K inhibitor BKM120 demonstrated synergy (54, 55). A phase I study combining these two agents has demonstrated anticancer activity of the combination in patients with recurrent HGSC or triple-negative breast cancer (56). Other PARPi combinations that have

demonstrated preclinical activity include combination with cyclin-dependent kinase (CDK) inhibitors (57) or with heatshock protein 90 (HSP90) inhibitors (58). These combinations may also provide strategies for overcoming PARPi resistance.

Combinations of antiangiogenics represent an attractive option for ovarian cancer treatment, yet these combinations appear to have increased toxicities. Combination of cediranib and olaparib demonstrated an increased incidence of hypertension, fatigue, and diarrhea compared with olaparib alone (53). The combination of cediranib and bevacizumab resulted in excess toxicities at doses beyond the recommended phase II dose (RP2D) of cediranib, 20 mg daily, and bevacizumab, 5 mg/kg every 2 weeks; central nervous system bleeding and severe hypertension were seen at doses above the RP2D (59). Other active antiangiogenic combinations have included sorafenib and bevacizumab; significant toxicities were also seen with this combination (60).

Additional combinations of biologics should be considered in ovarian cancer, especially inhibitors of pathways identified by the TCGA, immunotherapy agents, and antiangiogenics, thus mimicking the approaches taken with HIV therapy (61). Combination strategies are also being applied to other histologic subtypes of ovarian cancer; in LGSC, MEK inhibitors have demonstrated activity, and a combination of MEK inhibitors and PI3K inhibitors is currently being tested and has preclinical rationale (62). Ideally, because of the multiple permutations of combination biologic agents, these combinations should be tested preclinically before human phase I studies through use of ovarian cancer patient-derived xenografts or appropriate genetically engineered model systems (63, 64).

Other therapeutic areas of interest

Immunotherapy approaches are another area of therapeutic interest for ovarian cancer treatment. One of the earliest trials of ipilimumab was in recurrent ovarian cancer following administration of a GM-CSF-based vaccine (65). A recent presentation of nivolumab, an anti-PDL1 inhibitor, showed potential activity against recurrent ovarian cancer (66). Other newer agents of interest that show anti-ovarian cancer activity and are currently in clinical trials include antibody-drug conjugates such as DMUC5754A (anti-MUC16), DNIB0600A (anti-NaPi2b), and IMG853 (anti-folate receptor- α). Cyclin E1 (*CCNE1*) has also recently been identified as a potential target; *CCNE1* amplification is associated with platinum resistance and poor survival and has also been described as having synthetic lethality with *BRCA1/2* loss (67). These discoveries may represent opportunities for targeted therapy in this HGSC subtype.

The folate receptor is highly expressed in ovarian cancer; nonetheless, studies of agents that target the folate receptor have recently reported negative results. A phase III study of vintafolide (EC145), a folic acid-desacetylvinblastine conjugate that binds to the folate receptor, was stopped early because of futility in platinum-resistant ovarian cancer (68).

Farletuzumab, a humanized monoclonal antibody that binds to folate receptor- α , also failed to meet its primary PFS endpoint in patients with platinum-sensitive recurrent ovarian cancer (69). Despite these negative results, drugs targeting the folate receptor remain of interest in ovarian cancer drug development given its high expression levels.

In response to unique aspects of ovarian cancer, including the development of platinum resistance and the role of cancer stem cells and the tumor microenvironment, research efforts are leading to additional strategies for ovarian cancer (70, 71). Studies of agents that have been shown to reverse platinum resistance *in vitro* are ongoing; recent negative trials of current agents, such as phenoxidiol and decitabine, have also brought up questions of which clinical settings are most appropriate for testing these agents (72, 73). A recently reported randomized phase II study of the DNA hypomethylating agent 5-aza-2'-deoxycytidine (decitabine) in patients with partially platinum-sensitive cancer 6 to 12 months from their last platinum treatment found that the combination reduced the efficacy of carboplatin rather than increasing it (73). Focal adhesion kinase (FAK) inhibitors are another exciting class of drug currently in clinical trials (74, 75), and these agents exhibit both antiangiogenic effects and reversal of drug resistance.

Conclusions

Ovarian cancer is now considered to comprise different subtypes based on histology and molecular characteristics. This change has led to rational clinical trial design and positive trial results in specific ovarian cancer subtypes, such as those observed with PARPis in HGSC and MEK inhibitors in LGSC. Ultimately, in HGSC and in other histologic

subtypes, clinically translating available molecular information such as copy number alterations, gene expression data, and mutation information will be necessary to successfully improve treatment and future clinical trial development. Future and promising therapies include immunotherapies, new agents such as antibody–drug conjugates, and hypomethylating agents, as well as combinations of biologic agents with or without chemotherapy. Combinations of agents may be required to make meaningful gains in treating this cancer given its underlying genomic complexity. For more rare ovarian cancer subsets such as clear cell, mucinous, and LGSC, clinical trial design will require the cooperation of international groups to ensure rapid accrual to studies, and several collaborative international trials in these subtypes are already under way. In addition, commitment from the pharmaceutical industry is needed to study new agents in smaller subsets of patients, given the heterogeneity of ovarian cancer subtypes. This indeed is a very exciting time for ovarian cancer.

Authors' Contributions

Conception and design: J. Liu, U.A. Matulonis

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Grant Support

J. Liu is supported by a Liz Tilberis Early Career Award from the Ovarian Cancer Research Fund (258783) and the Pallotta Investigator Fund from the Dana-Farber Cancer Institute. U.A. Matulonis is supported by a Department of Defense Ovarian Cancer Award and Translational Project Award (W81XWH-12-1-0573 Log #OC110627), an Ovarian Cancer Research Fund Program Project Grant Award (292970), and a Breast Cancer Research Foundation 2013/2014 grant.

Received May 21, 2014; revised July 30, 2014; accepted July 31, 2014; published online October 15, 2014.

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