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New Strategies in Ovarian Cancer Treatment

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Abstract

Insights from basic science dissecting carcinogenesis in the fallopian tube and ovary have led to a deeper understanding of the origin, molecular characteristics, and types of ovarian cancers. This logically then has led to the development of novel approaches to treat ovarian cancer. Increasingly, novel agents are being developed to target the different growth pathways. The identification of molecular markers associated with different histopathologies has resulted in newer clinical trial designs to capture both clinical and translational endpoints. Unique molecular characteristics in DNA damage and repair pathways and unique cell surface markers have driven new drug development, yielding promise for both patients with platinum-sensitive and platinum-resistant ovarian cancers. Specific examples described include the histology-selective mutations, such as *ARID1A* in clear cell and endometrioid ovarian cancers; the rationale for using cell cycle checkpoint inhibitors when there already is a p53-mediated loss of cell cycle checkpoint regulation or combinations of agents that will both induce neoantigen formation and unleash immune modulators; and techniques to enhance the therapeutic delivery of known agents. A systematic and thoughtful approach to combining agents in clinical trials is needed so that irrespective of the trial outcomes, the results inform both clinical and translational endpoints.

Keywords

chemotherapy; combination therapy; microenvironment; new agents; ovarian cancer; targeted therapy

INTRODUCTION

Progress in the treatment of ovarian cancer has been exponential over the last decade, with a flurry of new experimental targeted agents and new drug approvals. With new opportunities come new challenges with regard to what agents to select, how best to evaluate those agents,

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and how best to identify optimal treatment regimens and improve patient outcomes. Several potential strategies for the development and application of new agents currently are being explored (Table 1).

For decades, different histologic diagnoses have been combined under the term “ovarian cancer” and treated in a similar fashion. The identification of specific molecular markers associated with different histologies has allowed for more accurate diagnoses. Those molecular markers or mutations also have led to, or themselves become, new targets for therapy. Thus, targeting the morphomolecular ovarian cancer type is one important strategy. The challenge has been in designing the clinical trials to provide sufficient information to help distinguish those mutations that drive cancer growth (potentially effective targets for treatment) from those mutations that create novel susceptibilities (potentially effective targets or target pathways), or that are passengers with no clinical value. New trial designs are another important tool to help answer translational and clinical questions. Translational questions can further refine the biologic understanding in a way that can inform which novel agents to use for different molecular subtypes of ovarian cancer.

Because the basic science of carcinogenesis in the fallopian tube and ovary has yielded many new insights, a variety of novel agents currently are in development to target either the tumor itself or the microenvironment in which it grows. A systematic and thoughtful approach to combining these agents in clinical trials is needed so that trial results, whether positive or negative, will inform both clinical and translational endpoints. This article discusses each of these strategies with concrete examples for ovarian cancer.

Morphomolecular Types

Ovarian cancer is not a single disease. The term has grown to include fallopian tube and primary peritoneal cancers, and furthermore is comprised of several morphomolecular types for which potential interventions may be more selective.[1] Table 2 lists the 5 major morphologic types of ovarian cancer and includes some key molecular and clinical characteristics.[2] Some of these characteristics have led to clinical precision medicine hypotheses. For example, the frequent mutations in *BRAF* and *KRAS* observed in patients with low-grade serous ovarian cancer (LGSOC) have led to several trials of MEK inhibitors, to our knowledge not all of which have been reported to date (ClinicalTrials.gov identifiers NCT02101788 and NCT01849874 and Farley et al[3]). The study of selumetinib[3] tested the hypothesis that patients with LGSOCs with *BRAF* or *KRAS* mutations would derive a benefit from MEK inhibition. This was posited because of constitutive active RAS/RAF signaling caused by the gain of function *KRAS/BRAF* mutations, when present. This single-arm study yielded a response rate of 15% and a median progression-free survival (PFS) of 11 months. However, the responses were not enriched in the patients whose cancers had mutations; in fact, the results demonstrated the opposite. The binimetinib study was stopped early for futility and to our knowledge the results have not been reported as of yet (ClinicalTrials.gov NCT01849874). One conclusion, pending information from the 2 outstanding studies, could be that activation of the MEK pathway may lead to sensitivity to MEK inhibition, although that may not be due to the activating BRAF and KRAS mutations.

Similarly, new information suggests that approximately 46% of clear cell[4] and 26% of low-grade endometrioid[5] ovarian cancers have loss of function (LOF) mutations in *ARID1A*, a member of the SWI/SNF chromatin remodeling complex. The LOF *ARID1A* mutation also has been found in adjacent endometriosis, thereby identifying a causative link in the pathogenesis of ovarian clear cell cancers.[6] This LOF contributes to cell death due to the inability to successfully repair DNA, leading to cell cycle arrest and cell death.[7] To our knowledge to date, there has been no successful *ARID1A*-directed therapeutic intervention, although cancers with *ARID1A* LOF mutations affect susceptibility to DNA-damaging agents. NRG-GY014 (ClinicalTrials.gov identifier NCT03348631), a study of tazemetostat (an EZH2 inhibitor), is poised to address *ARID1A* LOF as a target; accrual is limited to patients with clear cell cancers of the ovary and endometrium and will retrospectively evaluate outcome as a function of *ARID1A* mutation.

New Designs

Classic clinical trial designs are focused on the identification of the maximally tolerated dose, response rate, and outcome benefits. However, with the development of new agents and opportunities, it has become important to develop trial designs that may optimize information gathering to inform subsequent directions. Decisions regarding how and when to apply new agents and combinations should require compelling preclinical evidence; however, both preclinical and clinical testing creates a daunting task given the factorial number of combinations that can be envisioned and limited resources. Approaches, such as window of opportunity and platform studies, may allow for the broader and more rapid investigation of several directions concomitantly.[8,9] Platform studies can be broken down into 2 major components: baskets and umbrellas. Basket studies are used to examine an agent or combination of agents across many “baskets” of tumor types, whereas umbrella studies examine several regimens in one “umbrella” of patients.

The Nordic Society of Gynaecological Oncology (NSGO)–led OV-UMB1 study is an umbrella study of the concomitant examination of immune checkpoint inhibitor–containing combinations in patients with recurrent ovarian cancer (Fig. 1). This international academic collaboration tests novel doublets in a safety single-arm format with a predetermined stopping rule prior to the decision to proceed to randomization against standard of care. The current treatment arms are studying 3 different targeted combinations that incorporate durvalumab, an anti-programmed death–ligand 1 (PD-L1) agent. This approach leverages novel opportunities across a broad array of patients and may optimize early drug development for ovarian cancers.

New Agents

New agents and new approaches to therapeutic delivery also are on the horizon. A series of cell cycle checkpoint inhibitors currently are under development or already in clinical testing. Cells initiate a multitude of responses to protect the genome and ensure survival in response to DNA damage.[10] These responses include activation of cell cycle checkpoints causing subsequent cell cycle arrest to provide the cell with time to repair damaged DNA, and activation of the appropriate DNA repair mechanisms to efficiently complete repair. High-grade serous ovarian cancer (HGSOC) is characterized by universal p53 mutation, the

more common gain of function or a LOF null mutation, causing dysfunction of the p53-dependent G_1/S phase checkpoint.[11] Therefore, HGSOC relies heavily on G_2 checkpoint arrest to facilitate DNA damage repair, opening a new therapeutic opportunity for G_2/M targets.[11]

It has been hypothesized that the net effect of cell cycle checkpoint kinase 1 (CHK1), ataxia telangiectasia and Rad3-related (ATR), and WEE1 inhibition would be to push the cells through G_2 into early mitosis without successful DNA repair, thus causing mitotic catastrophe and cell death.[12] CHK1 is overexpressed in nearly all patients with HGSOC, making it a rational target to induce DNA damage and tumor cell death.[13] A recent phase 2 pilot study reported the efficacy of prexasertib, a second-generation CHK1 inhibitor, in heavily pretreated patients with *BRCA* wild-type, recurrent HGSOC (median, 5 prior therapies [range, 1–13 therapies]) yielding a 33% response rate and a median PFS of 7.4 months.[13] Preliminary bio-marker studies demonstrated that CCNE1 overexpression may be associated with response to CHK1 inhibition, but further research is needed to better characterize patients who derive a clinical benefit from treatment.

ATR is a central checkpoint protein kinase that is activated by single-strand DNA damage, including the resected ends of DNA double-stranded breaks and stalled replication forks. ATR activation induces a global shutdown of origin firing and slows down fork speed through activation of CHK1 and inactivation of cyclin-dependent kinases 1 and 2 (CDK1/2).[14] WEE1 kinase, which similarly is integral for the G_2 checkpoint, also keeps CDK1/2 inactive by phosphorylating CDK1/2 directly.[14] Currently, limited data regarding monotherapy for WEE1 or ATR inhibition are available but demonstrate an early signal of clinical activity in patients with ovarian cancer with deleterious *BRCA* mutations.[15]

G_2/M checkpoint inhibitors also may have greater success when combination approaches are used. Numerous preclinical data have suggested that the combination of cell cycle regulators (ATR, CHK1, and WEE1) with PARP inhibitors or cytotoxic chemotherapy limits the time allotted to repair DNA by restored homologous recombination repair, and promotes replication of damaged DNA, resulting in cell death.[11] For example, the WEE1 inhibitor adavosertib and PARP inhibition have been shown in numerous preclinical models to have greater benefit than either used alone, which may be due to the induction of replication stress within the background of DNA repair dysfunction.[16] Such preclinical findings have spurred several clinical trials combining PARP inhibitors and cell cycle inhibitors.[11] Treatment with the ATR inhibitor AZD6738 or prexasertib in combination with the PARP inhibitor olaparib currently is being tested in patients with recurrent ovarian cancer (ClinicalTrials.gov identifier NCT03462342) or in combination with olaparib in patients with solid tumors (ClinicalTrials.gov identifier NCT03057145). Pending clinical results will advance our understanding of the use of these new drugs, recognizing that the results may depend on trial design, clinical and molecular settings, and prior drug exposure.

Novel Combinations Targeting the Tumor and Tumor Microenvironment

Clinicians in the field of ovarian cancer learned early that any of the diseases under the ovarian cancer banner are not cured with single-agent therapy, that combination therapy yields greater activity of longer duration, and that disease recurs with potentially new

resistance mechanisms. That, coupled with intratumoral heterogeneity, has led researchers in several directions. First, and associated with numerous approvals worldwide, is the recognition that treating the (lymph)-angiogenic tumor microenvironment is an important element. The addition of bevacizumab has led to incremental benefits in PFS in patients undergoing primary therapy,[17,18] those with a first recurrence of platinum-sensitive disease,[19,20] and most notably in the AURELIA (A Study of Avastin (Bevacizumab) Added to Chemotherapy in Patients With Platinum-resistant Ovarian Cancer) study for patients with platinum-resistant ovarian cancer.[21] The most striking benefit of bevacizumab comes when one separates the balanced backbones of the AURELIA results, which demonstrated an improvement in PFS from 3.9 months to 10.4 months (hazard ratio [HR], 0.46) with the addition of bevacizumab to weekly paclitaxel. Similarly strong results were observed in the phase 2 trial of the addition of the VEGF receptor inhibitor cediranib to olaparib for women with platinum-sensitive disease[22,23]; the definitive phase 3 NRG GY004 trial currently is maturing and the results are expected this year. Both the Gynecologic Oncology Group (GOG)-0213 trial and the initial trial of the combination of cediranib and olaparib have demonstrated a trend and/or effect of the addition of the angiogenesis inhibitor for overall survival (HR, 0.83 [P=.056] and HR, 0.64 [P=.11], respectively).[20,23] To our knowledge, no overall survival advantage of the addition of antiangiogenic therapy has otherwise been demonstrated to date for ovarian cancer.

Another tumor microenvironment target is the immune microenvironment. To our knowledge, single-agent studies in patients with ovarian cancer have been disappointing to date.[24] Some benefit may be observed with the combination of ipilimumab and nivolumab, in which the single-agent nivolumab response rate of 12% (PFS of 2.0 months) increased to 33% (PFS of 3.9 months) with the addition of ipilimumab for the first 4 cycles (International Gynecologic Cancer Society NRG GY003 study). The PFS does not appear to be superior to that of historical controls (approximately 4 months), and toxicity must be considered. Numerous immunotherapy combinations with other immune checkpoint blockade agents, angiogenesis inhibitors, PARP inhibitors, and chemotherapy currently are underway across all stages of the tumor lifecycle. Some studies, such as that of the combination of avelumab with chemotherapy for patients newly diagnosed with and those with platinum-resistant recurrent ovarian cancer (JAVELIN [Avelumab and Talazoparib in Untreated Advanced Ovarian Cancer]-100, JAVELIN-100/PARP [talazoparib], and JAVELIN-200) were terminated early for futility. Accrual of >6000 women has been committed to a variety of randomized trials incorporating immunotherapy for newly diagnosed women, and a large number of studies also currently are ongoing for women with various recurrent states of disease. To our knowledge, there are limited preclinical data to support the use of these agents while recognizing a strong prognostic role for the ovarian cancer tumor immune context. The challenge is to define if and when immunotherapy should be used and the appropriate combination and sequence strategy at each point in the ovarian cancer life cycle, and to identify predictive biomarkers that will lead to tailored patient treatment.

It has been hypothesized that increased DNA damage by DNA repair inhibitors may promote local antigen release, resulting in systemic antitumor immune responses.[25] Such neoantigen release and high tumor mutational burden have been shown to be associated with clinical response to immune checkpoint inhibition in some solid tumors.[25] Preclinical data

have shown that the addition of PARP inhibitors to PD-1 blockade[26] or CTLA-4 inhibition[27] enhances antitumor activity in a *BRCA1*-deficient ovarian cancer mouse model. To our knowledge to date, limited clinical data are available from 3 active PARP inhibitor and PD-1 and/or PD-L1 blockade combination trials demonstrating early clinical activity in subsets of patients with recurrent ovarian cancer. A 72% response rate (RR) has been reported for durvalumab and olaparib in patients with germline *BRCA*-mutant, platinum-sensitive ovarian cancer[28]; a 25% RR has been reported for niraparib and pembrolizumab in patients with platinum-resistant ovarian cancer[29]; and a 14% RR has been reported for durvalumab and olaparib in heavily pretreated patients with ovarian cancer, predominantly composed of those with platinum-resistant *BRCA* wild-type disease.[30] In support, several phase 3 randomized trials of multipathway modulation (immune checkpoint inhibitor with or without PARP inhibition with or without VEGF inhibition) currently are being investigated in the frontline setting for ovarian cancer. In addition, a phase 2 single-arm study of durvalumab, olaparib, and cediranib currently is underway in patients with recurrent ovarian cancer (ClinicalTrials.gov identifier NCT02484404).

Improved Therapeutic Delivery

Attempts to improve activity while mitigating safety concerns have led to different approaches through which to bring injury to the tumor. Anatomic approaches such as hepatic intra-arterial drug administration have been explored. More recently, antibody-directed conjugates (ADCs) have been used. In this setting, a high-specificity antibody is loaded with a tumor-toxic payload. Focused targeting of agents has been successful in several venues, most notably the ADC trastuzumab-emtansine (TDM)-1 targeting a microtubule toxin through trastuzumab, an anti-HER2 antibody.[31]

Ovarian cancer has been shown to highly express folate receptor-α (FRα), with >70% of patients with HGSOC, approximately one-half of patients with LGSOC, and approximately one-third of patients with ovarian clear cell cancers reported as demonstrating positivity.[32] FRα had been targeted therapeutically in several ways, including through the use of direct antibody inhibition with farletuzumab,[33] and more recently with mirvetuximab soravtansine. Mirvetuximab soravtansine is an ADC in which a maytansine derivative is conjugated to the antibody in a nonhydrolyzable fashion.[34] Clinical development has been notable for the activity observed even in patients with ovarian cancer with low FRα expression, and side effects that included blurred vision related to keratopathy, fatigue, and diarrhea in the phase 1 study in women with recurrent ovarian cancer.[35] That cohort of 27 patients consisted of women who had an Eastern Cooperative Oncology Group performance status of 0 or 1, were heavily pretreated (median number of prior regimens, 4), and had platinum-resistant disease (74%). Their tumors had a range of FRα expression that was reflected in the RR, which was found to be highest for those with high receptor expression (5 of 16 patients) and no objective response was noted in those with low expression; the median PFS was highest for the patients demonstrating high expression (5.4 months). These data were believed to be encouraging and have led to several currently ongoing studies examining mirvetuximab soravtansine in combination with platinum, platinum combinations, and the FORWARD1 phase 3 registration trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer.[36] Thus, this example of targeting therapy to the cancer

cell specifically is encouraging as a new strategy for the treatment of patients with ovarian cancer.

Conclusions

A better understanding of the morphomolecular characteristics of ovarian cancer subtypes and the microenvironment in which the cancers grow has led to increased numbers of novel agents currently under consideration for the treatment of ovarian cancer. New trial structures already are being used to help define patient response to these novel agents in an efficient manner. This progress also has identified new challenges to overcome to optimize care further for the women we treat. Although trial recruitment is broad across age groups, the median age of the women in clinical trials is reported to be younger than that of women with ovarian cancer,[37] and a subset of women, as their cancer progresses or they experience increased comorbidities with age, often are too frail to participate safely in earlier phase clinical trials. This has defined an area of unmet need regarding how to provide for the frail and frail elderly appropriately so that they may participate in state-of-the-art trials.[38] The addition of changes in eligibility and the recognition of these important subsets of patients with unmet needs, coupled with new strategies and clinical trial designs, will advance opportunities, safety, and outcomes for women with ovarian cancer.

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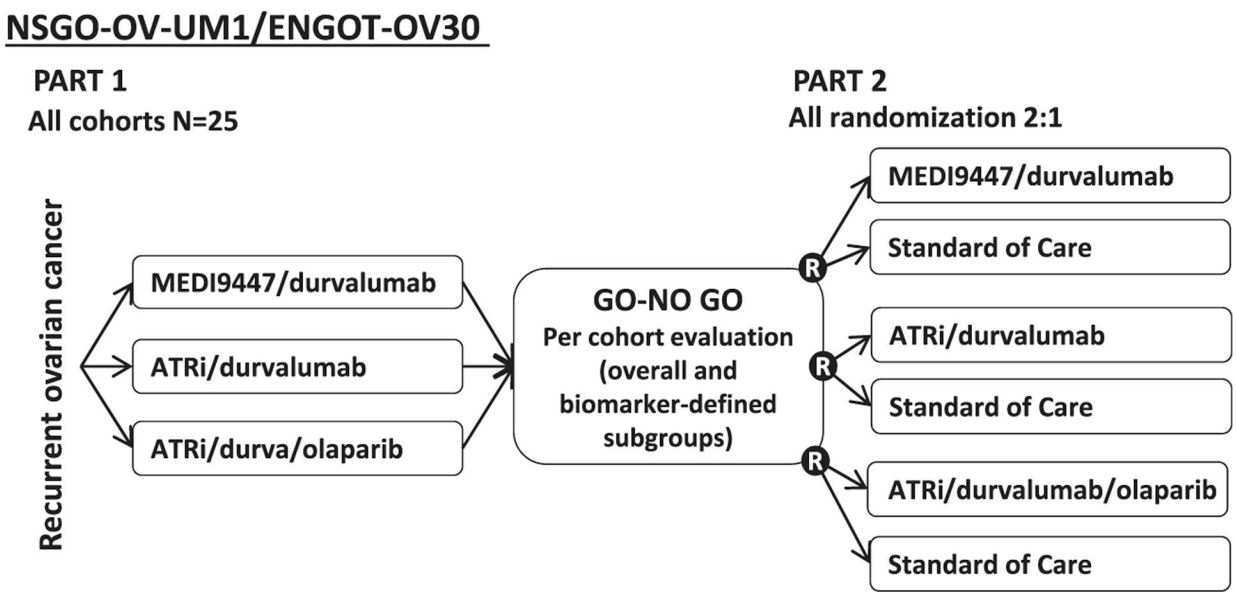

Figure 1.

The Nordic Society of Gynaecological Oncology (NSGO)-OV-UMB1 umbrella study. A different Gynecologic Cancer InterGroup clinical trials group is leading each arm and NSGO is the sponsor. Part 1 involves safety and initial activity assessment of the doublet. If the doublet passes the predetermined statistical target, it moves into a randomized phase 2 study against standard of care, using a 2:1 randomization (NSGO-OV-UM1/ENGOT-OV30). ATRi indicates ATR inhibitor; ENGOT, European Network for Gynaecological Oncological Trial.

TABLE 1.

Strategies for Optimizing the Treatment of OvCa

Strategy	Example
Targeting morphomolecular OvCa type	Different agents used to target HGSOC (chemotherapy, PARP inhibitors) vs LGSOC (MEK inhibitors, aromatase inhibitors)
New clinical trial designs	Umbrella studies
New agents	Examples of DNA damage and repair inhibitors: prexasertib, adavosertib, and ATRi
Novel combinations of agents that target the tumor microenvironment in addition to the tumor	Addition of antiangiogenic agents (bevacizumab, cediranib) chemotherapy or targeted agent and immune-therapy combinations
Improved therapeutic delivery	Antibody-directed conjugates Targeted radiotherapy

Abbreviations: ATRi, ATR inhibitor; HGSOC, high-grade serous ovarian cancer; LGSOC, low-grade serous ovarian cancer; OvCa, ovarian cancer.

TABLE 2.

Major Morphologic Types of Ovarian, Tubal, and Peritoneal Cancer

Type	Percent of Total	Molecular Characteristics	Clinical Characteristics
High-grade serous	70%	*TP53*^{mut}, *PIK3CA*^{mut} Copy number variability	Serous tubular in situ carcinoma[2] precursor; primary type in peritoneal carcinoma
Low-grade serous	3.5%	Approximately 50% *KRAS*^{mut} and approximately 20% *BRAF*^{mut}	Precursor is serous borderline cancer Frequent psammoma bodies
Clear cell	10%	*ARID1a*^{mut}, *PIK3CA*^{mut}, *PIK3CA*^{amp}	Endometriosis can transition into clear cell
Endometrioid high grade	10%	*ARID1a*^{mut}, *PIK3CA*^{mut}, *PTEN* LOH, *β-catenin*^{mut}	Can have borderline cancer precursor; some relationship to endometriosis
Endometrioid low grade		*TP53*^{mut}	Recategorized with high-grade serous
Mucinous	3.6%	80%$^{+}$ *KRAS*^{mut}	Intestinal type only; some question regarding whether this is observed only in borderline and early-stage disease; late stage presentation most commonly not ovarian primary tumor

Abbreviations: amp, amplification; LOH, loss of heterozygosity; mut, mutation.