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REVIEW

Anti-angiogenesis therapy, synthetic lethality, and checkpoint inhibition in ovarian cancer: state of the science and novel combinations

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Abstract

Over the last decade, new therapeutics in the form of anti-angiogenic treatment, synthetic lethality, and checkpoint inhibition have offered new options for the treatment of ovarian cancer. This review summarizes studies related to these treatment modalities and additionally novel combinations that offer a veritable therapeutic matrix for clinicians to choose from.

Keywords: bevacizumab, checkpoint inhibitor, chemotherapy, ovarian cancer, PARP inhibitor

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Introduction

In 2018, an estimated 22,240 women in the United States will be diagnosed with ovarian cancer; 14,070 women will die as a result of the disease.¹ With no formal screening available, the majority of women with ovarian cancer (80%) will present at an advanced stage of disease.² The method for treatment of ovarian cancer has remained much the same since the late 1990s. In the last decade, however, more research and alternate approaches to therapeutics have created a new horizon for the treatment of ovarian cancer.

Anti-angiogenesis

Anti-angiogenic therapy has become a new area of research within the last decade in the treatment of cancer. Neovascularization is essential to tumor survival and proliferation, and biomarkers for angiogenesis have become a hotbed of advancing research. Vascular endothelial growth factor (VEGF) presence is a known correlate to poorer outcomes in progression-free survival (PFS).³ Bevacizumab, a biologic therapy, is a recombinant humanized anti-VEGF monoclonal antibody. The primary complications of its use are hypertension (5–18%), bowel perforation (0.3–3%), hemorrhage (0.4–7%), and thromboembolism (5%).⁴

Data for a phase III trial examining bevacizumab's use in ovarian cancer – the Gynecologic Oncology Group, GOG-218, trial – were published in 2011.⁵ GOG-218 was a double-blind, placebo-controlled trial that enrolled women with stage III

disease with incomplete resection and stage IV disease under three arms. The control arm received paclitaxel 175 mg/m² of body-surface area and carboplatin at an area under the curve of 6, for cycles 1 through 6. The two bevacizumab groups were divided into 'initiation' and 'throughout' groups. Patients in the bevacizumab-initiation treatment arm received paclitaxel and carboplatin with bevacizumab (15 mg/kg of body weight) added in cycles 2 through 6 and placebo added in cycles 7 through 22. Bevacizumab-throughout treatment arm patients received paclitaxel and carboplatin with bevacizumab added in cycles 2 through 22. There was no difference in overall survival (OS) between the groups. The median PFS was 10.3 months in the carboplatin and paclitaxel control group, 11.2 months in the bevacizumab-initiation group, and 14.1 months in the bevacizumab-throughout group. Treatment with bevacizumab offered 4 additional months of PFS in this patient group. Data from GOG-218 regarding gastrointestinal (GI) adverse events indicated that the risk of GI adverse events is increased in those patients treated with bevacizumab and that the risk was further increased in those patients with a history of inflammatory bowel disease (IBD) and those with large or small bowel resection (LBR, SBR) at the time of treatment (relative odds, IBD: 13.4%, LBR: 2.05%, SBR: 1.95%, bevacizumab exposure: 2.15%).⁶ In May 2018, final OS data were released from GOG-218 in the intention-to-treat population. The relative hazard ratio (HR) for stage IV patients was reduced in those patients who received bevacizumab during frontline treatment and following (HR 0.774).⁷ Overall, no survival differences were found between those who received bevacizumab and chemotherapy versus

chemotherapy alone; however, those with stage IV disease may have a survival advantage with combination bevacizumab therapy with frontline chemotherapy and following.

Concurrent with GOG-218, the ICON7 ovarian cancer trial with bevacizumab in combination with standard chemotherapy was published. ICON7, however, additionally included women from stage I, II, or III following debulking and stage IV patients. ICON7 followed a different dosage schedule (7.5 mg/kg) every three weeks versus GOG-218, which administered double the dose at 15 mg/kg every three weeks.^{8,9} In addition to concluding the same results as GOG-218 with regard to PFS, ICON7 also revealed an improved OS to those patients deemed to have poor prognosis or high-risk disease (stage IV disease, inoperable stage III, or suboptimally debulked stage III disease). The increase in OS for those in the high-risk category was approximately 9 months.

In 2012, data from the phase III, randomized, multicenter, blinded, placebo-controlled OCEANS trial were released, comparing bevacizumab with gemcitabine and carboplatin to gemcitabine and carboplatin alone in those patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer. PFS was significantly improved in those patients who had received bevacizumab (median PFS 12.4 to 8.4 months).¹⁰

In 2017, results of the bevacizumab group from the GOG-213 trial were released, which evaluated use of bevacizumab in those patients with platinum-sensitive ovarian cancer who have recurrence after completion of initial therapy. The dosing of bevacizumab was the same as in GOG-218 (15 mg/kg) and women were assigned to either carboplatin/paclitaxel alone or with bevacizumab. Median OS was improved in the bevacizumab group (42.2 versus 37.3 months)¹¹; however in intention-to-treat analysis, this benefit was not found to be statistically significant.

Bevacizumab has also been studied for use in the platinum-resistant group. In 2014, results for the AURELIA trial were released, which analyzed bevacizumab with chemotherapy in platinum-resistant ovarian cancer. Median PFS was 3.4 months in the chemotherapy alone group (pegylated liposomal doxorubicin, weekly paclitaxel or topotecan) versus 6.7 months in the chemotherapy plus bevacizumab group.¹²

Following the release of GOG-218 and ICON7 data, the National Comprehensive Cancer Network (NCCN) labeled the first-line use of bevacizumab in ovarian cancer as a category 3 recommendation. In Europe, under the European Medicines Agency (EMA), use of bevacizumab was approved for first-line use following the results of GOG-218. In practice, the dosages are those given in the ICON7 trial, as there is a lower cost and toxicity associated with that. At the time of this writing, ICON 8B has accrued nearly three quarters of patients required for the study of PFS and OS in first-line treatment of ovarian cancer with dose-dense carboplatin-paclitaxel and bevacizumab.¹³

In the fall of 2017, Genetech, a member of Roche pharmaceuticals, submitted a supplemental biologics license

application (sBLA) for Avastin® (bevacizumab), in combination with paclitaxel and carboplatin followed by bevacizumab for frontline treatment of advanced ovarian cancer. The US Food and Drug Administration (FDA) approved this application on June 13, 2018, nearly two weeks ahead of the Prescription Drug User Fee Act (PDUFA) date of June 25, 2018.¹⁴ The application was submitted with data based on the results of the GOG-0218 phase III trial. When approved, this will represent a change in the bedrock regimen for ovarian cancer that has not changed since the 1990s when platinum-based chemotherapy doublets became standard of care for frontline treatment.

Cost has been a primary barrier for access and approval for bevacizumab both in the United States and in Europe. Cost evaluation as relating to GOG-218 and ICON7 of bevacizumab supporting the category 3 recommendation by the NCCN was particularly grim. One study found that in accounting for treatment cost and treatment related to adverse events, the PFS increase found with bevacizumab was not cost effective.¹⁵ The study examined incremental cost-effectiveness ratios (ICERS) per progression-free life-year saved (PF-LYS). The cost of standard therapy of paclitaxel and carboplatin for 600 patients as modeled on arms of GOG-218 was US\$2.5 million, standard therapy plus bevacizumab cost US\$21.4 million, and it cost US\$78.3 million in the standard therapy plus bevacizumab plus bevacizumab maintenance.¹⁵ Data taken from the same study with prospective data were published in 2015 to include quality-of-life measurements with the similar conclusion that frontline bevacizumab was not cost effective.¹⁶ Encouragingly, however, data revealed that the ICER value of standard therapy and bevacizumab plus bevacizumab maintenance fell below 100,000 per PF-LYS when the cost of bevacizumab was reduced to 25% of baseline cost.

With the approval for Amgen's biosimilar for bevacizumab, Mvasi®, in September 2017, it appears that cost, while not erased as a concern, will be less of a vanguard issue in its frontline use. Mvasi has not yet attained approval for ovarian cancer as Roche, a Swiss multinational pharmaceutical company and maker of Avastin, still has an orphan drug exclusivity for bevacizumab in ovarian cancer indications until 2021. In addition, 15 biosimilars to bevacizumab have been announced for testing within the last 5 years.

Additional information has also been garnered from the GOG-218 study, which may spur further research in identifying new targets for therapy and understanding responsiveness to chemotherapy. A paper outlining response to bevacizumab in those patients with mutations in homologous recombination repair (HRR) genes describes that in those patients who have HRR defects, including BRCA wild-type patients; however, the benefit of bevacizumab addition was not increased in this population particularly.¹⁷ Another retrospective analysis of biomarkers in patients who participated in GOG-218 suggested a positive correlation between cellular expression of VEGF-A and cellular targets

of anti-VEGF (CD31) and improvement in PFS and OS with treatment of bevacizumab.¹⁸

Synthetic lethality

Another exciting target that has garnered attention in the ovarian cancer field are poly (ADP-ribose) polymerases, or PARPs. Many PARP enzymes have now been identified and work is still being completed to understand the entire enzyme family. These enzymes are integral to deoxyribonucleic acid (DNA) repair in the cell cycle. In those patients who have BRCA mutations, PARPs are critical to the survival and proliferation of tumor cells. In addition to blocking their activity and preventing single strand DNA repair in tumor cells that have deficient repair homologous recombination systems (BRCA1/BRCA2), the PARP inhibitors also induce the localization of the PARP enzymes to the DNA strand, preventing further replication.¹⁹ This type of induced cell death is known as synthetic lethality, where a combination of deficiencies in gene expression leads to cell death.

Olaparib

The first of these inhibitors is olaparib. Olaparib (Lynparza[®]) is approved for the following: (1) the monotherapeutic treatment of germline BRCA-mutated (gBRCAm) ovarian cancer in patients who have failed three or more prior courses of chemotherapy and (2) the monotherapeutic maintenance of recurrent ovarian cancer in those patients who are in complete or partial response to platinum-based chemotherapy regardless of BRCA status. In 2014, results from Study 42 demonstrated results from olaparib used as monotherapy in patients with germline BRCA1/2 mutation and recurrent BRCA1/2-associated cancers, including platinum-resistant ovarian cancer patients. The tumor response rate in ovarian cancer patients was 31.1% and 40.0% had stable disease lasting longer than 8 weeks.²⁰ In 2014, olaparib became the first PARP inhibitor in the United States to be approved for germline-mutated, BRCA-positive advanced ovarian cancer for patients who have received three or more prior lines of chemotherapy.

In 2012, Study 19 released results for olaparib maintenance therapy in those patients with platinum-sensitive, relapsed ovarian cancer with or without the BRCA1/2 mutation. The study confirmed that median PFS was significantly increased in the olaparib group including non-BRCA positive patients: 11.2 versus 4.3 months.²¹ Subsequent analyses of these data proved that those patients who were BRCA1/2 positive had a better response to olaparib.²² In 2014, based on results from Study 19, approval for olaparib in the maintenance setting for those patients with BRCA mutations was garnered in the European Union.

In 2017, final results from a double-blind, randomized, placebo-controlled phase III trial for olaparib as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation known as SOLO2/ENGOT-Ov21 were released.²³ Patients were required to have BRCA1/2 mutation,

normal organ and bone marrow function, no brain metastases, no other malignancies, platinum-sensitive disease, and had received two prior lines of platinum-based chemotherapy with current response. There were 295 patients from 123 sites in 16 countries who were randomized to receive either olaparib maintenance therapy (300 mg twice daily) or matching placebo pills twice daily. Primary endpoints were PFS as defined by objective radiological disease progression or death using modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The data were analyzed by both the investigators and an independent group. With both analyses, the olaparib group benefited from significantly prolonged PFS when compared to the placebo group (19.1 months, 95% confidence interval [CI]: 16.3–25.7 versus 5.5 months CI: 5.2–5.8). Importantly, quality-of-life measures were similar in both groups. In 2017, following release of SOLO2, the FDA approved the use of olaparib for maintenance treatment for patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.²⁴

In June 2018, the makers of olaparib, AstraZeneca, made public in a press release the data from SOLO-1, a randomized controlled trial examining olaparib as a maintenance monotherapy for those patients with the BRCA mutation following complete or partial response to platinum-based therapy.²⁵ The patients who received olaparib instead of placebo had statistically and clinically significant improvements in PFS compared to those patients who did not receive olaparib.²⁶ Final data for SOLO-1 were released in October 2018. Results from this trial exceeded expectations and final data demonstrated a 70% decrease in disease progression compared to placebo. The FDA in response has granted an accelerated review for olaparib in the frontline maintenance setting and expected response is due in the first quarter of 2019.

SOLO-3 (NCT02282020)^{27,28} will examine 266 patients in a phase III trial to assess efficacy of olaparib versus physician's choice single-agent chemotherapy for those patients with platinum-sensitive, relapsed ovarian cancer with BRCA1/2 mutations. The primary outcome for this study is objective response rate. Estimated completion date is set for January 2019.

Olaparib is dosed twice daily in oral tablet or capsule form. For those patients who have failed three or more prior courses of chemotherapy and olaparib is a consideration for monotherapeutic treatment, there is a companion diagnostic for determination of the eligibility and BRCA status: BRACAnalysis CDx[®]. The most common nonhematologic side effects of olaparib include nausea and fatigue; the most common hematologic side effects are anemia and neutropenia. The most serious side effects of olaparib are myelodysplastic syndrome and acute myelogenous leukemia; estimated incidence is 1–3%.^{20,29}

Rucaparib

The second PARP inhibitor approved by the FDA for treatment of ovarian cancer was rucaparib (Rubraca[®]) in 2016. Rucaparib is

approved for the following: (1) for treatment in BRCA-positive patients who have failed two or more lines of chemotherapy and (2) maintenance treatment in those women with ovarian cancer who are in complete or partial response to platinum-based chemotherapy.

In January 2017, results from ARIEL 2 Part 1 trial were released. The study described use of rucaparib in relapsed, platinum-sensitive, high-grade ovarian cancer.³⁰ In addition to BRCA1/2 data, this study also used genomic loss of heterozygosity (LOH) as a marker for homologous recombination deficiency (HRD). Patients with LOH greater than 14% were determined to belong in LOH high category. There were 206 patients who were treated with oral rucaparib (600 mg twice per day) until disease progression as determined by RECIST criteria. Primary outcome for analysis was PFS. The patients were divided into subcategories based on BRCA mutant, BRCA wild-type and LOH high, BRCA wild-type and LOH low categories, and BRCA wild-type and LOH unclassified. Median PFS with rucaparib was 12.8 months (95% CI: 9–14.7) in the BRCA mutant group, 5.7 months in the LOH high subgroup, and 5.2 in the LOH low subgroup. ARIEL3, a phase III trial, published later that year, found similar evidence to support use of rucaparib for maintenance treatment following platinum-based therapy in women with platinum-sensitive, relapsed, high-grade, serous ovarian, endometrioid ovarian, fallopian tube, and primary peritoneal cancer.³¹ At the same time, ARIEL2 results were released, and results from Study 10, a phase I–II study of rucaparib in BRCA-positive ovarian cancer patients, revealed that rucaparib was simultaneously safe and efficacious in those patients with platinum-sensitive, relapsed ovarian cancer with BRCA mutation.³² The FDA approved the companion diagnostic for rucaparib, FoundationFocusCDx®.

Based on results of ARIEL3, the FDA in early 2018 approved rucaparib for use as maintenance treatment for women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. ARIEL4 is a phase III confirmatory trial with an estimated primary completion date of 2022; it will evaluate rucaparib against standard-of-care chemotherapy in women who have had at least two prior chemotherapy regimens.³³ The most common side effect of rucaparib is fatigue. Rucaparib is dosed orally, twice daily. As with olaparib, rucaparib does carry a slight risk of myelodysplastic disorder and acute myelogenous leukemia. As of yet, rucaparib has yet to be approved for those patients who have wild-type BRCA.

Niraparib

Niraparib (Zejula®) is the latest PARP inhibitor that has been granted approval for use in ovarian cancer by the FDA. Niraparib is approved for the maintenance treatment for those with recurrent ovarian cancer in complete or partial response to platinum-based chemotherapy. In a phase III trial, ENGOT-OV16/NOVA, niraparib was studied in patients with platinum-

sensitive, recurrent ovarian cancer.³⁴ Like ARIEL2, NOVA also identified markers of HRD in those patients with wild-type BRCA. This determination was made by tumor tissue samples and HRD, determined as positive or negative based on a molecular classifier developed by Myriad Genetics. The test, known as myChoice®, is an integrated genome-based assay for HRD that quantitates genomic instability of the tumor and also classifies BRCA1/2 variants. The primary endpoint was PFS. Patients received 300 mg of niraparib daily versus placebo. In those patients who had a germline BRCA mutation, PFS was 21.0 versus 5.5 months in the placebo group. In the nongermline mutation group, median PFS was 9.3 versus 3.9 months versus the placebo group. In those patients who had tumors with HRD, the median PFS was 12.9 versus 3.8 months.

Follow-up studies from NOVA include the QUADRA study, which examined niraparib in those patients with recurrent platinum-sensitive ovarian cancer with positive HRD status.³⁵ Results from the QUADRA study were recently presented at the American Society of Clinical Oncology. There were 463 patients who had received at least three lines of chemotherapy and measurable disease consistent with RECIST imaging criteria who were enrolled in the study, including platinum-refractory, platinum-resistant, and platinum-unknown response patients. In those patients who were HRD positive and platinum sensitive, the overall response rate (ORR) was 29% with a duration of response (DOR) of 9.2 months. Among BRCA-positive patients who were either platinum sensitive or resistant/refractory and being treated in the fourth-line setting and beyond, ORR was 31% and the median DOR was 9.4 months.

The FDA granted approval for use of niraparib in those patients who have wild-type BRCA and do not have HRD, as the PFS also was increased in a statistically significant way for patients in this group. Patients who receive niraparib do not need to have proven BRCA mutation or HRD deficiency. The most common side effects of this once-daily drug are hematologic in origin and include thrombocytopenia, anemia, neutropenia, and leukopenia. Other common side effects include GI side effects like nausea, vomiting, constipation, dyspepsia, and decreased appetite. Retrospective analysis of the NOVA trial has also been helpful in analyzing weight as a possible predictor of grade 3 and 4 treatment-emergent adverse events and dose reduction. Those patients whose weight was below 58 kg had a greater incidence of adverse effects, requiring a dose reduction, with only 13% of these patients able to continue on the once-daily 300 mg dose, and the incidence of thrombocytopenia was 43%.³⁶

Other PARP inhibitors, veliparib and talazoparib, are currently being studied in the treatment of ovarian cancer. GOG 3005 is a phase III, randomized, controlled trial for those patients with newly diagnosed ovarian cancer who receive standard platinum-based therapy and veliparib. Talazoparib has thus far been examined in phase I and II trials for those with BRCA-mutated cancers and other advanced cancer types.

Checkpoint immunotherapy

Most recently, checkpoint immunotherapy has also become a target for the treatment of ovarian cancer. Checkpoint inhibitors function by removing a tumor's defense from the body's immune system and/or induce immunologic response. There are two specific targets that are currently being studied for ovarian cancer: programmed death-1 (PD-1) and T lymphocyte-associated antigen 4 (CTLA-4). Currently, there are a number of anti-PD-1 or antiprogrammed death ligand (anti-PD-L1) inhibitors being studied for the treatment of ovarian cancer and two anti-CTLA-4 inhibitors. PD-1 is a protein expressed by tumor specific T cells; when this protein interacts with PD-L1 as expressed by normal cells and tumor cells, T cells are not activated. By inhibiting this interaction, tumor cells are robbed of their disguise and able to be recognized by the body's immune system. Currently there is only one checkpoint inhibitor, pembrolizumab, approved for use in those patients with ovarian cancer. Pembrolizumab is approved for those whose tumors histologically reveal high microsatellite instability (MSI-H) or mismatch-repair deficient (dMMR) and have received prior treatment without satisfactory alternative options. This approval however is nonspecific and approved for use in solid tumors that have high MSI.

While numerous checkpoint inhibitors are currently under development for study, the current drugs with trials close to reporting and that prevent the interaction between PD-1 and PD-L1 are nivolumab, pembrolizumab, avelumab, durvalumab, and atezolizumab. Additionally, ipilimumab (an anti-CTLA4) is a checkpoint inhibitor examined in the context of ovarian cancer treatment. Phase II studies have been completed for nivolumab and the safety profile has been found to be acceptable for those with platinum-resistant ovarian cancer.³⁷ The drug was found to have encouraging results in a group of 20 patients, two of whom had complete response. Avelumab has undergone phase I and II studies and the JAVELIN Ovarian 100 study is a phase III multicenter investigation of avelumab in combination with and/or following platinum-based chemotherapy with the primary goal of analyzing avelumab alone as a maintenance agent or in combination with platinum maintenance.³⁸

Moving forward and novel combinations

Perhaps most exciting is that with the debut of these new methods of treatment, novel combinations for ovarian cancers have become available. Exciting combinations with multiple targets such as anti-angiogenesis therapeutics combined with PARP inhibitors or checkpoint modulators have created veritable matrices of selection for treatment of ovarian cancer.

Newly diagnosed treatment/maintenance

In PAOLA-1 (NCT02477644), researchers have begun recruitment for the phase III study of platinum, taxane, and bevacizumab with

or without olaparib in newly diagnosed patients with advanced stage ovarian cancer (IIIB–IV) regardless of BRCA status. PAOLA-1 will include 612 participants and is due to be completed in 2022.³⁹ The primary endpoint to be examined is PFS.

In IMagyn-50 (NCT03038100), a planned 1300 patients with newly diagnosed stage III or IV ovarian cancer will undergo platinum therapy and bevacizumab with or without atezolizumab, a checkpoint inhibitor.⁴⁰ Groups will include those undergoing primary tumor-reductive surgery followed by chemotherapy and those undergoing neoadjuvant therapy followed by interval surgery and continued chemotherapy treatment. Primary endpoints will include PFS and OS.

In OVARIO (NCT03326193), researchers will be examining the response to bevacizumab and niraparib as maintenance therapy in 90 patients, following frontline platinum therapy in combination with bevacizumab and at least one prior attempt at tumor debulking surgery. This is a phase II trial with the primary endpoint being PFS at 18 months.

In the FIRST trial (NCT03307785), a 4-part phase II study is being undertaken to examine the safety and efficacy of niraparib plus the checkpoint inhibitor TSR-042 (a humanized monoclonal antibody that acts on PD-1), carboplatin-paclitaxel plus SR-042, niraparib plus bevacizumab plus TSR-042, and carboplatin-paclitaxel plus bevacizumab plus TSR-042.⁴¹ The trial will enroll 102 women with advanced or metastatic disease with primary outcome measures being safety and tolerability of each of these combinations; secondary outcome measures will include ORR and DOR.

The ATHENA trial (NCT03522246) is a phase III trial evaluating rucaparib and nivolumab in the maintenance context following response to frontline platinum-based therapy after cytoreductive surgery (either primary or interval debulking).⁴² Four arms will be examined for patients with newly diagnosed advanced International Federation of Gynecology and Obstetrics (FIGO stage III–IV): oral rucaparib plus IV nivolumab, oral rucaparib plus IV placebo, oral placebo plus IV nivolumab, oral placebo plus IV placebo. The study has an estimated enrollment of 1012 patients, and the primary outcome for the study is PFS.

Platinum-sensitive recurrence

The Javelin PARP Medley study (NCT03330405) is a large study that will examine avelumab in combination with talazoparib in patients with locally advanced metastatic (primary or recurrent) solid tumors: non-small cell lung cancer, triple-negative breast cancer, hormone-receptor positive breast cancer, urothelial cancer, castration-resistant prostate cancer, and recurrent platinum-sensitive ovarian cancer.⁴³ Experimental arms C1 and C2 will include patients with recurrent platinum-sensitive ovarian cancer, while experimental arm F will include those advanced solid tumors with BRCA or ataxia telangiectasia mutation (ATM) defect regardless of primary or recurrent status. As this is a multiphase study, phase II dosing will be dependent on the data from the 1b portion of the study.

The MEDIOLA (NCT02734004) study is a phase I/II study of durvalumab (MEDI4736) and olaparib with or without bevacizumab in those patients with gBRCAm, platinum-sensitive, relapsed ovarian cancer, relapsed small cell lung cancer, and gBRCAm metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer.⁴⁴ With a planned 288 patients, researchers will use disease control rate, safety, and tolerability as outcome measures.

In 2016, trial NRG-GY004 (NCT02446600) began recruitment of 549 patients for a phase III trial comparing olaparib or a combination of cediranib and olaparib to standard platinum-based chemotherapy in women with recurrent platinum-sensitive ovarian cancer.⁴⁵ Cediranib is a VEGF receptor 1–3 inhibitor whose effects were studied in ICON6, which found increased PFS, and an incremental benefit in OS when long-term survival outcomes were analyzed.^{46,47} The trial arms will include platinum-based chemotherapy, olaparib alone, or olaparib plus cediranib. Estimated primary completion date is scheduled at the end of 2019. Primary outcome measure will be PFS.

ATALANTE (NCT02891824) is a phase III study with a plan to study 405 patients with platinum-sensitive ovarian cancer in the setting of recurrence, using treatment of atezolizumab with bevacizumab and platinum-based chemotherapy.⁴⁸ This is a two-prong study with placebo plus bevacizumab plus platinum-based chemotherapy and atezolizumab plus bevacizumab plus platinum-based chemotherapy. Primary outcome will be PFS.

Platinum-resistant recurrence

TOPACIO (NCT02657889)/KEYNOTE-162 is a phase I/II study that will evaluate the combination of niraparib and pembrolizumab in patients with advanced or metastatic triple-negative breast cancer or recurrent ovarian cancer.⁴⁹ The primary outcome measure for phase I will be dose-limiting toxicities; for phase II the primary outcome will be ORR. Estimated completion is set for 2019.

The CONCERTO trial (NCT02889900)⁵⁰ phase IIb study will enroll 100 patients who have platinum-resistant disease in the setting of having received at least three or more prior lines of chemotherapy and do not carry a BRCA mutation, to receive cediranib and olaparib. The primary outcome measure will be ORR.

Cediranib and olaparib will also be studied in combination in the phase II/III NRG-GY005 (NCT02502266)⁵¹ trial for 680 patients with recurrent platinum-resistant ovarian cancer regardless of BRCA type, unless clear cell, mixed epithelial, undifferentiated carcinoma, or transitional cell carcinoma histology is identified, in which case patients are eligible if BRCA mutation is discovered. The phase III portion of the study will include three arms: physician's choice standard-of-care chemotherapy, cediranib plus olaparib, or single-agent, either cediranib or olaparib.

In study NRG-GY009 (NCT02839707),⁵² atezolizumab and bevacizumab in combination with doxorubicin will be studied as treatment for 488 patients with platinum-resistant disease. This phase II/III study has three arms: pegylated liposomal doxorubicin

hydrochloride (PLD) plus atezolizumab, PLD plus bevacizumab plus atezolizumab, and PLD plus bevacizumab. Primary outcome measures are dose-limiting toxicities, PFS, and OS.

In EORTC-1508 (NCT02446600),⁵³ atezolizumab, bevacizumab, and acetylsalicylic acid will be examined as treatment for 160 patients with platinum-resistant disease. This is a phase II study with five arms: bevacizumab, atezolizumab plus placebo, atezolizumab plus acetylsalicylic acid, atezolizumab plus bevacizumab plus placebo, and atezolizumab plus bevacizumab plus acetylsalicylic acid. Primary outcome for this study will be PFS at 6 months.

In JAVELIN Ovarian 200 (NCT02580058),⁵⁴ avelumab alone or in combination with PLD will be studied as treatment for 566 patients with platinum-resistant or refractory ovarian cancer. This is a phase III study with three arms: avelumab alone, avelumab plus PLD, and PLD alone. Primary outcome measures will be OS and PFS up to approximately 20 months.

Recurrence (regardless of platinum-sensitivity status)

In phase II NRG-GY003 (NCT02498600),⁵⁵ 96 patients with persistent or recurrent ovarian cancer will be randomized to receive nivolumab or nivolumab plus ipilimumab. Primary outcome of this study will be objective tumor response as assessed by RECIST criteria measured on a weekly basis.

A phase I/II study for the combination of olaparib plus tremelimumab in BRCA1/2 mutation carriers with recurrent ovarian cancer has also begun, with an estimated completion date set in 2022.⁵⁶ A planned 50 patients will be given olaparib plus tremelimumab. The primary outcome for phase I of the study will be recommended dose and in phase II PFS measured up to 5 years will be the primary outcome measure.

Conclusion

With encouraging success using anti-angiogenesis agents and PARP inhibitors, and new synthetic lethality targets emerging almost monthly from bench research, the options for treatment of ovarian cancer have burgeoned. In an area of treatment that has remained relatively stable for the last decade, new treatment types are a welcome and exciting change in a disease process whose prognosis is grim. With the above improved armaments for treatment of ovarian cancer, targeted therapy has become an exciting frontier with PARP inhibitors providing significant improvement in PFS, especially in those with BRCA1 and BRCA2 mutations. Anti-angiogenesis has now been validated in all settings with the newly diagnosed, platinum-sensitive, and platinum-resistant populations. The future treatment for ovarian cancer treatment now will include clinical research results from checkpoint immunotherapy and combinations of targeted therapy, with advances of bench research into predictive biomarkers, antibody-drug conjugates, stem cell identification and eradication, gene therapy, and with innovations to come in CRISPR (clustered regularly interspaced short palindromic repeats) delivery.

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