

# Updates and New Options in Advanced Epithelial Ovarian Cancer Treatment

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The medical and surgical treatment strategies for women with epithelial ovarian cancer continue to evolve. In the past several years, there has been significant progress backed by landmark clinical trials. Although primary epithelial ovarian cancer is still treated with a combination of surgery and systemic therapy, more complex surgical procedures and novel therapeutics have emerged as standard of care. Cytotoxic chemotherapy and maximal surgical effort remain mainstays, but targeted therapies are becoming more widespread and new data have called into question the role of surgery for women with recurrent disease. Poly ADP-ribose polymerase inhibitors have improved progression-free survival outcomes in both the frontline and recurrent settings, and their use has become increasingly widespread. The recent creation of treatment categories based on genetic changes reinforces the recommendation that all women with epithelial ovarian cancer have germline genetic testing, and new biomarker-driven drug approvals indicate that women may benefit from somatic molecular testing as well. To continue to identify novel strategies, however, enrollment on clinical trials remains of the utmost importance. With the evolving data on surgical approaches, targeted therapies such as antiangiogenics and poly ADP-ribose polymerase inhibitors, and the new therapeutic agents and combinations in development, we hope that advanced epithelial ovarian cancer will eventually transition from an almost universally fatal disease to one that can increasingly be cured.

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Ovarian cancer remains the gynecologic cancer responsible for the most deaths each year in industrialized countries; in 2020, it is estimated that

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21,750 new cases and 13,940 deaths will occur in the United States<sup>1</sup> and 29,000 deaths will occur in Europe.<sup>2</sup> The majority of patients with epithelial ovarian cancer are diagnosed with advanced-stage disease.<sup>3</sup> Although there have been many significant advances in the treatment of epithelial ovarian cancer over the past several decades, recurrent ovarian cancer remains an almost uniformly fatal disease. Of those diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage (2014) III or IV ovarian cancer, more than 70% will have a recurrence of their disease within the first 5 years.<sup>4</sup> Because the clinical need is arguably greatest for these patients, our focus here is on the treatment of advanced disease.

Several algorithms have been designed for screening both average-risk and high-risk patients,<sup>5–7</sup> but these have been of limited utility. Most new cases of ovarian cancer are initially diagnosed by gynecologists and primary care physicians. Pelvic masses may be found on examination or during work-up for a nonspecific symptom such as pelvic pain, gastrointestinal symptoms, or bloating, or during a visit to the

emergency department for severe symptoms. Once a pelvic mass is identified, in the absence of disseminated disease, laboratory tests such as a CA 125 or an integrated serum panel<sup>8–10</sup> may help determine which patients should be referred to a gynecologic oncologist for surgery. Of note, however, these integrated panels, like CA 125, should not be used for screening either the general population or women at high risk for ovarian cancer. For patients diagnosed after surgery with a gynecologist, consultation with a gynecologic oncologist and a formal tumor board discussion is highly recommended to determine whether additional surgery or adjuvant therapy may be indicated. Indeed, outcomes are best when women with gynecologic cancers are treated by a gynecologic oncologist.<sup>11</sup>

Even for primary adjuvant treatment there is no longer a single best treatment algorithm and several patient specific clinico-pathologic parameters and genomic results factor into the treatment decisions. As the disease progresses, the treatment choices become increasingly complex. The past few years have brought many new considerations to the treatment of women with epithelial ovarian cancer, and 2020 has brought the additional challenge of treating patients with ovarian cancer during the coronavirus disease 2019 (COVID-19) pandemic. For gynecologic oncologists faced with an increasing amount of high-quality literature, deciding on an ideal next therapy requires a nuanced weighing of the risks and benefits of many new treatment modalities and combinations. The purpose of this review is to summarize the current standard of care and highlight recently published, high-impact studies that may change the future care for women with epithelial ovarian cancer.

## PRIMARY TREATMENT

The outlook on the surgical debulking of advanced ovarian cancer is evolving as we continue to refine the scope and timing of primary surgery and chemotherapy. However, the importance and relevance of surgical effort for the survival of the patient remains evident. The volume of residual disease after debulking surgery is still the strongest prognostic factor for progression-free survival and overall survival.<sup>12</sup> Primary debulking surgery is generally preferred, but neoadjuvant chemotherapy followed by interval debulking surgery is an alternative for a certain subset of patients, such as those who are older, women with a large disease burden, or those with multiple comorbidities.<sup>13,14</sup> During the past 10 years, two trials were published which suggested no difference between a primary and interval tumor debulking.<sup>15,16</sup> However,

some oncologists cite concerns regarding the generalizability of these findings.<sup>17</sup> A 2020 phase III study from Japan failed to show noninferiority of neoadjuvant chemotherapy compared with primary debulking surgery,<sup>18</sup> and another phase III cooperative group trial evaluating this question in high-volume centers is planned.<sup>17</sup> Defining the most appropriate patients for primary debulking has been difficult, and multiple scoring systems have been proposed.<sup>19,20</sup>

Regardless of the timing of the procedure, maximal debulking effort remains the standard of care, and research suggests that patients are often willing to trade some increase in perioperative complications and mortality in exchange for a potential increase in overall survival.<sup>21</sup> Operations generally include bilateral salpingo-oophorectomy, hysterectomy, infracolic and infragastric omentectomy, and resection of any other gross visible disease. Surgery of advanced disease often includes some combination of pelvic or abdominal peritonectomy, bowel resection, splenectomy, and diaphragm stripping. Comprehensive staging, including multiple biopsies and lymph node dissection, is more important in patients with early stage disease that grossly appears confined to the ovary or pelvis. For patients with apparent stage III or IV disease, the lack of benefit for routine lymphadenectomy was recently clarified in the LION phase III trial, published in 2019. The study enrolled 647 patients with macroscopically completely resected ovarian cancer and compared survival outcomes in those with systematic pelvic and para-aortic lymph node dissection and those with no lymph node dissection.<sup>22</sup> Surprisingly, there was no difference in progression-free survival or overall survival between the two approaches, but there was a higher incidence of complications with the systematic lymph node dissection. Of note, 56% of women had positive lymph nodes. Based on these results, it is no longer our practice to perform a systematic lymph node dissection for patients with advanced stage disease at diagnosis. Instead, we evaluate the retroperitoneal spaces and only remove grossly enlarged lymph nodes that are either palpated intraoperatively or noted on preoperative imaging.

For more than two decades, standard chemotherapy for primary ovarian cancer has included a combination approach using carboplatin and paclitaxel.<sup>23</sup> Most commonly, doublet chemotherapy in the primary setting is administered once every 3 weeks, but this changed for many oncologists after a 2013 study from the Japanese Gynecologic Oncology Group found that weekly paclitaxel was associated with improved outcomes.<sup>24</sup> However, neither the

Gynecologic Oncology Group (GOG) 262 study in 2016<sup>25</sup> nor the British ICON8 phase III trial published in 2019<sup>26</sup> could replicate those findings. Historically, frail patients were often treated with single-agent platinum. Now combination therapy should be strongly considered for older patients with poor performance status. At the American Society of Clinical Oncology 2019 Annual Meeting, results from the randomized EWOC-1 trial suggested that frail, elderly patients who received a combination of paclitaxel and carboplatin had improved outcomes when compared with the group that received single-agent carboplatin (Falandry C, Savoye AM, Stefani L, Tinquaut F, Lorusso D, Herrstedt J, et al. EWOC-1: a randomized trial to evaluate the feasibility of three different first-line chemotherapy regimens for vulnerable elderly women with ovarian cancer (OC): a GCIG-ENGOT-GINECO study [abstract]. *J Clin Oncol* 2019;37 (15 suppl):5508. doi: 10.1200/JCO.2019.37.15\_suppl.5508). One exception to carboplatin and paclitaxel treatment, however, may be for women with mucinous ovarian cancer, a rare histologic subtype. These women may derive more benefit from gastrointestinal-type chemotherapy regimens as compared with traditional carboplatin-based regimens.<sup>27,28</sup>

In 2006, intraperitoneal chemotherapy became a standard of care in North America, when GOG 172 was published. The investigators found a 16-month overall survival benefit for women who received intraperitoneal chemotherapy compared with those who received intravenous chemotherapy.<sup>29</sup> This study's findings were reevaluated in a 2018 phase III clinical trial that also incorporated the use of an angiogenesis inhibitor, bevacizumab. In GOG 252, two intraperitoneal arms (intravenous dose dense paclitaxel plus intraperitoneal carboplatin compared with intravenous and intraperitoneal paclitaxel plus intraperitoneal cisplatin) and a dose dense intravenous arm of carboplatin and paclitaxel were compared.<sup>30</sup> Patients in all three arms received bevacizumab concomitant with chemotherapy and as maintenance. No significant advantage in progression-free or overall survival was observed in optimally resected patients with stage III disease given either intraperitoneal chemotherapy regimen compared with the intravenous-only arm after a median follow-up of 85 months.<sup>30</sup> Moreover, intraperitoneal chemotherapy had higher toxicity than intravenous carboplatin and paclitaxel with bevacizumab. The reason for the differences in outcomes between the two studies is unknown, but some hypothesize that it may be related to some combi-

nation of new factors compared with the original study, such as the dose dense paclitaxel administration, the lower dose of cisplatin, the shorter paclitaxel infusion time length, or the addition of bevacizumab. Although we still offer intraperitoneal chemotherapy after primary tumor reductive surgeries using the original GOG 172 protocol, including inpatient administration of paclitaxel over 24 hours as an inpatient, its use is much less frequent, because many patients do not desire the increased toxicity and treatment intensity, especially in light of less certain improvement in clinical outcomes.

Building on the above historic rationale for intraperitoneal chemotherapy, there has recently been a growing interest in the use of hyperthermic intraperitoneal chemotherapy for women with primary ovarian cancer. Hyperthermic intraperitoneal chemotherapy has already been implemented in other peritoneal malignancies such as appendiceal and gastric cancers and, therefore, it was rational to assess this treatment in women with ovarian cancer. In a recent Dutch phase III trial, patients with FIGO stage III epithelial ovarian cancer who had responded to three cycles carboplatin and paclitaxel were randomized to interval debulking surgery with or without hyperthermic intraperitoneal chemotherapy, using heated (40°C) intraperitoneal cisplatin at the time of surgery.<sup>31</sup> Both groups received three more cycles of carboplatin and paclitaxel postoperatively. Hyperthermic intraperitoneal chemotherapy was associated with an improved recurrence-free survival (14 vs 11 months) and overall survival (46 vs 34 months) when compared with the standard treatment arm with comparable complication rates. Although this study was small (N=245 patients), the significant benefits found were intriguing. Criticisms of the study included its open-label trial design, concerns about differences in surgical effort or approach between the two arms, lack of a nonheated intraperitoneal comparator arm, and narrow patient enrollment criteria, which probably resulted in a study group that was not representative of the general population of patients with epithelial ovarian cancer. Furthermore, concerns were raised about the increased complexity and cost of intraoperative chemotherapy.<sup>32,33</sup> A phase III trial by the same group, which will address some of these criticisms, is planned.<sup>34</sup> However, in the interim, our current practice is to discuss hyperthermic intraperitoneal chemotherapy at interval debulking with the subgroup of patients with FIGO stage III disease who are recommended to have neoadjuvant chemotherapy, because outcomes for this high-risk subset of patients remains poor.

## POLY (ADP-RIBOSE) POLYMERASE INHIBITORS AS MAINTENANCE THERAPY AFTER PRIMARY CHEMOTHERAPY

Poly (ADP-ribose) polymerase inhibitors are a new class of drugs that have added an exciting treatment option for women with ovarian cancer. Poly (ADP-ribose) polymerase inhibitors interfere with the ability of tumor cells to repair DNA damage, and therefore are particularly effective in the subset of tumors with existing impairment of DNA repair functions. Recently, patients with high-grade serous ovarian cancer have been classified into four categories related to DNA repair. The first category includes women who have a germline mutation in *BRCA1* or *BRCA2* or other DNA repair-related genes (eg, *PALB2*, *RAD51C*, *ATM*).<sup>35</sup> The second category includes women who do not have any of these germline genetic changes, but their tumors have somatic (tumor) mutations in one of the DNA repair genes. The third group of women has tumors that do not have a somatic mutation but are classified as homologous recombination deficient. This classification includes tumors with loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions (chromosomal breaks between adjacent regions of at least 10 Mb).<sup>36</sup> In practice, homologous recombination deficiency usually includes patients in all three of the first, second and third categories, although their outcomes may be different. The fourth category includes women whose tumors show no detectable impairment of DNA repair functions using current assays. This last group includes about 50% of patients with high-grade serous ovarian cancer.

Initially, indications for poly (ADP-ribose) polymerase inhibitor use in patients with ovarian cancer were limited to patients with germline or somatic tumor *BRCA* mutations in the recurrent setting. However, in 2018, poly (ADP-ribose) polymerase inhibitors were introduced to front-line treatment (Table 1). The SOLO1 phase III study enrolled 391 patients with high-grade advanced serous or endometrioid ovarian cancer and a *BRCA1* or *BRCA2* mutation (germline or somatic).<sup>37</sup> To enroll in the trial, patients must have had a response to platinum-based chemotherapy. At 3 years of follow-up, 60% of patients in the group who took the maintenance oral poly (ADP-ribose) polymerase inhibitor (olaparib) were disease-free, compared with only 27% of patients who took placebo pills. The risk of disease progression or death was 70% lower with olaparib treatment. Survival data were not mature at the time of reporting (21% mature) but at 3 years, 20% of patients in the placebo group

had died compared with 16% of those in the olaparib group.<sup>37</sup> In 2018, these data led the U.S. Food and Drug Administration (FDA) to approve olaparib maintenance therapy for frontline in patients with ovarian cancer with germline or somatic *BRCA1* or *BRCA2* mutations.

Subsequently, several other trials have evaluated the use of poly (ADP-ribose) polymerase inhibitors as maintenance therapy after the completion of primary adjuvant therapy in patients whose tumors had a good response to chemotherapy (Table 1). In the phase III PRIMA trial, 733 patients with high-grade advanced serous or endometrioid ovarian cancer that responded to platinum-based chemotherapy were randomly assigned to maintenance treatment with niraparib or placebo after initial adjuvant chemotherapy.<sup>38</sup> In homologous recombination-deficient cancers, including those with *BRCA* mutations, progression-free survival was longer with niraparib maintenance (22 vs 10 months). In homologous-recombination proficient tumors, the progression-free survival was shorter, but still significantly improved (8.1 vs 5.4 months). The treatment benefit of niraparib on progression-free survival extended to all subgroups: neoadjuvant chemotherapy (14 vs 8 months); complete response to chemotherapy (16 vs 10 months); partial response to carboplatin and paclitaxel (8 vs 6 months).<sup>38</sup> This led to an FDA approval in April 2020 for the use of niraparib as a maintenance therapy in women with advanced epithelial ovarian cancer who have had a complete or partial response to primary platinum-based chemotherapy.

VELIA was a phase III placebo-controlled trial that included 1,140 patients with high-grade advanced serous ovarian cancer.<sup>39</sup> Women were randomized to platinum-based chemotherapy (control), platinum-based chemotherapy with veliparib followed by placebo maintenance, or platinum-based chemotherapy with veliparib and veliparib maintenance therapy (veliparib throughout). Doses of veliparib used concomitantly with chemotherapy were lower than those used for maintenance. Of note, the chemotherapy with veliparib followed by placebo maintenance arm compared with the control arm was not included as a primary outcome but was included as a secondary endpoint. In patients with germline or somatic *BRCA* mutations, progression-free survival in the group that received veliparib throughout was 35 months compared with 22 months in the control group; in patients with homologous recombination-deficient cancers (including those women with *BRCA* mutations) progression-free survival was 32 compared with 21 months. In the entire cohort, the progression-free

**Table 1. Summary of Phase III Clinical Trials for Primary Maintenance Poly (ADP-ribose) Polymerase Inhibitor Therapy**

Trial Name	Eligibility Criteria	Arms	Findings
SOLO1 <sup>37</sup>	High-grade serous or endometrioid Germline or somatic <i>BRCA1</i> or <i>BRCA2</i> mutation Stage III or IV Complete or partial response to chemotherapy Received platinum-based chemotherapy without bevacizumab Required tumor debulking if stage III; required tumor debulking or primary biopsy if stage IV	Olaparib	Median progression-free survival (olaparib vs placebo):
		Placebo	Overall cohort (germline or somatic <i>BRCA</i> mutations): Not reached vs 13.8 mo (HR 0.30, 95% CI 0.23–0.41, <i>P</i> <.001)
PRIMA <sup>38</sup>	High-grade serous or endometrioid Subgroup with homologous recombination deficiency (HRD) ( <i>BRCA</i> mutation or score higher than 42 on myChoice test); other subgroup included those with proficient or unknown HRD status Stage III or IV Complete or partial response to chemotherapy Received at least 6–9 cycles of chemotherapy Required to have had residual disease after surgery, received neoadjuvant therapy, or be inoperable if stage III, or any stage IV	Niraparib	Median progression-free survival (niraparib vs placebo):
		Placebo	HRD cohort: 21.9 vs 10.4 mo (HR 0.43, 95% CI 0.31–0.59, <i>P</i> <.001)  Overall cohort: 13.8 vs 8.2 mo (HR 0.62, 95% CI 0.50–0.76, <i>P</i> <.001)
PAOLA-1 <sup>43</sup>	High-grade serous or endometrioid, or other nonmucinous epithelial histology with germline <i>BRCA</i> mutation Any <i>BRCA</i> mutation status, any HRD status Stage III or IV Complete or partial response to chemotherapy Received bevacizumab as part of treatment Not required to have had tumor debulking; any debulking outcome allowed	Olaparib, bevacizumab maintenance	Median progression-free survival (olaparib vs placebo):  Overall cohort: 22.1 vs 16.6 mo (HR 0.59, 95% CI 0.49–0.72, <i>P</i> <.001)  Somatic <i>BRCA</i> mutation cohort: 37.2 vs 21.7 mo (HR 0.31, 95% CI 0.20–0.47)  Somatic <i>BRCA</i> wildtype cohort: 18.9 vs 16.0 mo (HR 0.71, 95% CI 0.58–0.88)
		Placebo, bevacizumab maintenance	HRD cohort (score 42 or higher): 37.2 vs 17.7 mo (HR 0.33, 95% CI 0.25–0.45)  HRD positive, wildtype somatic <i>BRCA</i> cohort: 28.1 vs 16.6 mo (HR 0.43, 95% CI 0.28–0.66)
			HRD negative or unknown cohort: 16.9 vs 16.0 mo (HR 0.92, 95% CI 0.72–1.17)
VELIA <sup>39</sup>	High-grade serous Any <i>BRCA</i> mutation status, any HRD status Stage III or IV Enrolled before chemotherapy 6 cycles of chemotherapy Required to have had tumor debulking	Carboplatin, paclitaxel, veliparib with veliparib maintenance	Median progression-free survival (veliparib throughout vs placebo throughout):  Germline <i>BRCA</i> mutation: 34.7 vs 22.0 mo (HR 0.44, 95% CI 0.28–0.68, <i>P</i> <.001)
		Carboplatin, paclitaxel, veliparib with placebo maintenance	HRD tumors (score 33 or higher): 31.9 vs 20.5 mo (HR 0.57, 95% CI 0.43–0.76, <i>P</i> <.001)
		NOTE: this arm was not included in the primary outcome	Overall cohort (intention to treat): 23.5 vs 17.3 mo (HR 0.68, 95% CI 0.56–0.83, <i>P</i> <.001)
		Carboplatin, paclitaxel, placebo with placebo maintenance	

HR, hazard ratio; HRD, homologous recombination deficient.

survival advantage was 24 compared with 17 months.<sup>39</sup> A preliminary analysis of the secondary objective comparing veliparib with chemotherapy only and the control group found no differences in progression-free survival for any of the subgroups of patients with ovarian cancer at the time of the database lock. Of note, in this trial, the hazard ratio for progression-free survival for veliparib throughout compared with control was 0.80 (95% CI 0.64–1.00) for all *BRCA* wildtype tumors and 0.81 (95% CI 0.60–1.09) for non-homologous recombination-deficient tumors (both non-statistically significant). This suggests that the homologous recombination deficiency assay (Myriad myChoice) used did not select those who would benefit among patients lacking a tumor *BRCA* mutation. It is possible that use of the assay depends on context, and that its use in all-comers (as in VELIA) may be less informative than use only in those with platinum-sensitive disease. Also of note, VELIA was the only phase III trial of a poly (ADP-ribose) polymerase inhibitor that included concomitant use during the initial cytotoxic chemotherapy (as noted above, veliparib was dose reduced during the combination phase). Although other poly (ADP-ribose) polymerase inhibitors have been combined with cytotoxic backbones, toxicity (particularly bone marrow toxicity) makes the combination difficult to administer.<sup>40–42</sup>

A fourth phase III trial that combined a poly (ADP-ribose) polymerase inhibitor with an antiangiogenic agent in the frontline maintenance setting was presented in 2019 (Table 1). PAOLA-1 evaluated the combination of bevacizumab and olaparib in 806 patients with high-grade advanced serous or endometrioid ovarian cancer, who had a response to platinum-based chemotherapy plus bevacizumab.<sup>43</sup> For the overall population, patients randomized to bevacizumab and placebo maintenance had a 17-month progression-free survival compared with 22 months in patients receiving bevacizumab and olaparib. Patients with *BRCA* mutations had the largest benefit, a progression-free survival of 37 months with olaparib and bevacizumab compared with 22 months with bevacizumab single agent maintenance. Patients with homologous-recombination proficient tumors did not benefit from the combination (progression-free survival of 16 vs 17 months).<sup>43</sup> This study led the FDA to approve the combination of bevacizumab and olaparib as frontline maintenance therapy for women who had a complete or partial response to platinum-based chemotherapy and whose tumors are homologous recombination deficient. We anticipate that this will be the preferred option for patients

whose tumors demonstrate homologous recombination deficiency and who were already receiving bevacizumab during adjuvant chemotherapy.

In summary, trials consistently show a progression-free survival benefit of poly (ADP-ribose) polymerase inhibitors as maintenance therapy in the first-line treatment of high-grade serous and endometrioid ovarian cancers. As a result, there are now three FDA approvals for poly (ADP-ribose) polymerase inhibitor maintenance therapy in the frontline setting. This has led to a practice shift where many women will now be treated with poly (ADP-ribose) polymerase inhibitor maintenance therapy in the frontline setting. It must be noted, however, that we do not yet have mature overall survival results from any of the trials, and these future results may ultimately change our practice patterns again.<sup>37–39,43</sup>

### ANTIANGIOGENIC THERAPY IN THE PRIMARY SETTING

Antiangiogenic therapy in ovarian cancer has been studied for two decades. Gynecologic Oncology Group 218 was a pivotal phase III trial studying 1,873 patients with incompletely resected advanced stage ovarian cancer.<sup>44</sup> Patients received either carboplatin and paclitaxel (control), carboplatin and paclitaxel with concurrent bevacizumab and placebo maintenance or carboplatin-paclitaxel with bevacizumab and bevacizumab maintenance. Based on the initial GOG 218 results, which showed a 4-month improvement in progression-free survival with concurrent and maintenance bevacizumab therapy, the FDA approved bevacizumab for front-line use in stage III or IV ovarian cancer in 2018. However, in 2019, updated results that analyzed 9 years of follow-up showed that there was no overall survival benefit with concurrent and maintenance bevacizumab added to standard chemotherapy.<sup>45</sup> Two studies published within the past 2 years evaluated two newer oral antiangiogenic agents, pazopanib and nintedanib, in the primary maintenance setting and showed similar results.<sup>46,47</sup> Both studies demonstrated a small progression-free survival benefit associated with use of the oral antiangiogenic agents without any difference in overall survival. However, in an exploratory subset analysis of patients with FIGO stage IV tumors, GOG 218 results suggest that concomitant and maintenance bevacizumab treatment may be beneficial (there was a 10-month improvement in overall survival vs patients in a control group). Moreover, the final overall survival results of the phase III British ICON7 trial showed an overall survival benefit of bevacizumab treatment in patients who were at

highest risk for disease progression (stage IV, suboptimally debulked stage III, or inoperable stage III disease).<sup>48</sup> In our practice, we reserve frontline bevacizumab use for patients who have had suboptimal tumor debulking, patients with stage IV disease, or those who have had a poor response or are refractory to frontline carboplatin and paclitaxel chemotherapy.

## TREATMENT OF RECURRENT OVARIAN CANCER

### Surgical

Historically, surgery for recurrent ovarian cancer was considered for women with platinum-sensitive disease who had a relatively long tumor-free interval (at least six, but preferably 12 months) after completion of chemotherapy and who had isolated or small-volume disease and minimal ascites. Gynecologic Oncology Group 213 was the first prospective study to address the benefits of surgery for recurrent disease. Women with platinum-sensitive, recurrent ovarian cancer deemed amenable to complete tumor resection were randomized to chemotherapy alone (with or without bevacizumab) or secondary surgical cytoreduction and chemotherapy (with or without bevacizumab).<sup>49</sup> The results showed that secondary debulking offered no improvement in progression-free or overall survival. Some oncologists have raised concerns that patients for whom surgery was thought to be most beneficial (eg, those with oligometastatic disease to the retroperitoneal lymph nodes or spleen) might not have been enrolled on this trial in the first place owing to physician bias, but a subanalysis of those patients on GOG 213 who had a single site of disease still did not show improvement with surgery.

A second trial evaluating the role of secondary debulking was initially presented in 2017 (DESKTOP III) and did demonstrate a 5 month improvement in progression-free survival (19.6 vs 14.0 months) favoring the surgery arm (Bois AD, Vergote I, Ferron G, Reuss A, Meier W, Greggi S, et al. Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20 [abstract]. *J Clin Oncol* 2017;35(15 suppl):5501. doi: 10.1200/JCO.2017.35.15-suppl.5501). Patients were eligible if they had an excellent functional status (Eastern Cooperative Oncology Group performance status of 0), less than 500 mL of ascites, and a complete resection after their primary cytoreductive procedure. Overall survival data were presented at the American Society of Clinical Oncology 2020 Annual Meeting, and demonstrated an improvement in both

progression-free (18.4 vs 14.0 months) and overall survival (53.7 vs 46.2 months) (Bois AD, Sehouli J, Vergote I, Ferron G, Reuss A, Meier W, et al. Randomized phase III study to evaluate the impact of secondary cytoreductive surgery in recurrent ovarian cancer: final analysis of AGO DESKTOP III/ENGOT-ov20 [abstract]. *J Clin Oncol* 2020;38(15 suppl):6000. doi: 10.1200/JCO.2020.38.15-suppl.6000). However, the results also demonstrated that in patients who had an incomplete resection of their tumor, those who had surgery had shorter overall survival than those who did not have surgery. Given these conflicting and nuanced findings, enough uncertainty remains regarding the benefit of secondary cytoreduction for women with platinum-sensitive ovarian cancer at the time of their first recurrence that we believe that it is a treatment option to consider in select patients for whom complete resection is considered to be likely. We are very restrictive in our selection criteria, and perform secondary debulking procedures only on patients with single site disease and good performance status. We do not re-operate on patients with platinum-resistant disease, miliary disease, or ascites.

### Systemic Therapy

Most patients with recurrent ovarian cancer are treated with cytotoxic chemotherapy during the course of their disease. The current standard of care for first-line treatment of platinum-sensitive, recurrent, ovarian cancer is a carboplatin-containing combination. Frequently used doublet combinations include liposomal doxorubicin, gemcitabine, or a taxane. Several studies have demonstrated an approximately 4-month improvement in progression-free survival with the addition of bevacizumab.<sup>50,51</sup> A phase III clinical trial in patients with platinum-sensitive ovarian cancer published earlier this year compared patients given carboplatin, gemcitabine, and bevacizumab (the standard group) compared with those given carboplatin, liposomal doxorubicin, and bevacizumab (the experimental group).<sup>52</sup> The authors found a small progression-free survival benefit (13.3 vs 11.6 months,  $P=.01$ ), as well as a small overall survival benefit (31.9 vs 27.8 months,  $P=.03$ ) in the experimental (liposomal doxorubicin) group. Many studies have evaluated a variety of single-agent cytotoxic combinations for platinum-resistant ovarian cancer, and multiple options are listed in the National Comprehensive Cancer Network guidelines.<sup>53</sup> Our practice is to incorporate bevacizumab into certain single-agent treatments (eg, weekly paclitaxel, topotecan, liposomal doxorubicin), particularly if it had not previously been administered, because the AURELIA

trial demonstrated a statistically significant, 3-month improvement in progression-free survival<sup>54</sup> as well as an improvement in quality of life for the use of bevacizumab in the setting of platinum-resistant disease.

The use of poly (ADP-ribose) polymerase inhibitors in the recurrent setting has also become much more widespread. Three poly (ADP-ribose) polymerase inhibitors have been approved by the FDA as a treatment line for patients with recurrent ovarian cancer: olaparib, rucaparib, niraparib.<sup>53</sup> When they are used as single agents in the setting of germline or tumor (somatic) *BRCA* mutations, platinum sensitivity is the strongest indicator that a patient will benefit from treatment. In addition, single-agent olaparib yielded improved progression-free survival and response rates compared with nonplatinum chemotherapy in women with germline *BRCA* mutations and platinum-sensitive relapsed disease.<sup>55</sup>

In 2017, three randomized phase III trials also showed that maintenance therapy after initial response to platinum-based treatment with each of these three poly (ADP-ribose) polymerase inhibitors was associated with an improved progression-free survival in patients with platinum-sensitive recurrent ovarian cancer.<sup>56–58</sup> Olaparib, rucaparib, and niraparib were all approved by the FDA for maintenance treatment of women with platinum-sensitive recurrent ovarian cancer, regardless of the tumor's biomarker status. At the 2020 American Society of Clinical Oncology Annual Meeting, updated data from the SOLO2 trial were presented showing a statistically significant improvement in overall survival for women treated with olaparib maintenance therapy (hazard ratio 0.74, 95% CI 0.54–1.00) (Poveda A, Floquet A, Ledermann JA, Asher R, Penson RT, Oza AM, et al. Final overall survival (OS) results from SOLO2/ENGOT-ov21: a phase III trial assessing maintenance olaparib in patients (pts) with platinum-sensitive, relapsed ovarian cancer and a *BRCA* mutation [abstract]. *J Clin Oncol* 2020;38(15 suppl):6002. doi: 10.1200/JCO.2020.38.15\_suppl.6002). On this updated analysis, however, 8% compared with 4% of the patients receiving olaparib and placebo, respectively, developed myelodysplastic syndrome. This is higher than in previous analyses, which were closer to 1%,<sup>37,58,59</sup> and will be an important consideration as increasing numbers of patients are treated with poly (ADP-ribose) polymerase inhibitors earlier in their treatment sequence and for longer periods of time. A 2020 analysis evaluated additional exploratory endpoints in rucaparib maintenance therapy: time to subsequent therapy, time to disease progression when on the subsequent therapy, and chemotherapy-free inter-

vals. These results suggested that the benefit of the therapy persisted past the initial improvement in progression-free survival associated with maintenance therapy.<sup>59</sup> However, the progression-free survival benefits were strongest for women with germline *BRCA* mutations or those who had tumors demonstrating homologous recombination deficiency. In our practice, we perform next-generation sequencing on tissue from the initial debulking surgery at the time of recurrence if it has not yet been done. However, because the primary maintenance indication for poly (ADP-ribose) polymerase inhibitor therapy now includes women with somatic *BRCA* mutations, we obtain this information regularly in the upfront setting when possible. Tests to determine whether a tumor has homologous recombination deficiency are commercially available and are companion diagnostics to several FDA indications. Historically, we did not frequently order these tests owing to their cost, logistical constraints, and their limited usefulness given the approvals for any recurrent platinum-sensitive disease. Additionally, recent data are emerging that suggest that the identification of specific alterations rather than the homologous recombination deficiency score itself may be more predictive of tumor behavior.<sup>60</sup> However, with the new frontline maintenance indications, we now discuss tumor homologous recombination deficiency evaluations with patients if their tumors are negative for specific (*BRCA1*, *BRCA2*, *PALB2*) homologous recombination deficiency-associated mutations on both germline and somatic testing. It is important to note, however, that the reported studies occurred in women who had never before been treated with poly (ADP-ribose) polymerase inhibitors. With the recent frontline approvals, the utility of retreatment with a poly (ADP-ribose) polymerase inhibitor becomes an important unanswered question. Although a small retrospective study suggested that a few patients may still benefit from retreatment (Essel K, Behbakht K, Lai T, Hand L, Evans E, Dvorak J, et al. PARPi after PARPi in epithelial ovarian cancer [abstract]. *Gynecol Oncol* 2019;154 (suppl 1):6. doi: 10.1016/j.ygyno.2019.04.022), a larger, prospective trial addressing this question is ongoing (NCT03106987).

Poly (ADP-ribose) polymerase inhibitors in combinations with other agents are also being evaluated in the recurrent treatment setting. The combination of niraparib and bevacizumab was evaluated in an open-label, randomized, phase II trial (AVANOVA2) that included 97 patients with high-grade advanced serous–endometrioid, platinum-sensitive, recurrent ovarian cancer.<sup>61</sup> Patients receiving niraparib with bevacizumab had a progression-free survival of 12



months compared with 6 months with niraparib alone. Progression-free survival was also improved in the subgroup of patients without *BRCA* mutations: 11 months for the combination compared with 4 months with niraparib alone. Side effects in both groups included anemia, fatigue, and gastrointestinal disturbances. Proteinuria and hypertension were manageable side effects found more frequently in the combination group.

The most common side effects of poly (ADP-ribose) polymerase inhibitors include hematologic toxicities (anemia, thrombocytopenia, neutropenia), gastrointestinal symptoms (nausea, vomiting, diarrhea), and fatigue. Hematologic toxicities are often managed with dose interruptions and reductions, but occasionally transfusions are needed for severe anemia or thrombocytopenia. Gastrointestinal symptoms can frequently be managed with supportive measures such as antiemetics. Creatinine elevations have been reported, but appear to be related to the inhibition of renal transporters rather than true renal impairment.<sup>62</sup> Therefore, it is advisable to perform a glomerular filtration rate scan study before discontinuing therapy for an elevated creatinine. In general, poly (ADP-ribose) polymerase inhibitors are well-tolerated by patients treated in the recurrent setting and adverse effects are often easily addressed. Indeed, the reanalysis of data from a prior phase III study revealed that patients treated with maintenance niraparib had a longer asymptomatic period than those managed with routine surveillance.<sup>63</sup> As more patients are treated with maintenance poly (ADP-ribose) polymerase inhibitor therapy, it is increasingly important to evaluate multiple quality-of-life considerations, such as cost, tolerability, and long-term adverse effects including myelodysplastic syndrome.<sup>64,65</sup> These considerations are especially important in the upfront setting, because the time between adjuvant therapy and a patient's first recurrence is often the longest treatment-free interval after diagnosis.

Immunotherapy has proved effective in a number of recurrent cancers but has been less successful for patients with ovarian cancer. The most prevalent immunotherapy agents available in oncology currently are checkpoint inhibitors, most frequently targeting PD-1, PD-L1, and CTLA-4, although novel checkpoints are currently under investigation. In a phase II study of pembrolizumab, an immune checkpoint inhibitor of PD-1, objective response rates for patients with recurrent ovarian cancer did not exceed 10%.<sup>66</sup> Given these disappointing outcomes, the recent focus of early-phase clinical trials in patients with recurrent ovarian cancer has shifted toward com-

binations that incorporate immunotherapy with the goal of sensitizing tumors to the effect of immunotherapy. A phase II trial of patients with recurrent ovarian cancer that compared use of nivolumab (an immune checkpoint inhibitor of PD-1) as a single agent or combined with ipilimumab (a checkpoint inhibitor of CTLA-4) found similarly disappointing activity in the single-agent nivolumab arm with an objective response rate of 12%.<sup>67</sup> However, 31% of the combination group had an objective response, which was significantly greater than those who received nivolumab alone.<sup>67</sup> A phase I–II study of the combination of the poly (ADP-ribose) polymerase inhibitor, niraparib, and pembrolizumab for patients with platinum-resistant recurrent ovarian cancer showed a disappointing median progression-free survival of 3.4 months, and an objective response rate of 18% (90% CI 10–28%).<sup>68</sup> Currently, many other studies of novel combinations that include immunotherapy agents are ongoing.

When possible, our practice is to encourage patients with recurrent ovarian cancer to enroll in clinical trials. In the absence of an appropriate clinical trial, we refer to National Comprehensive Cancer Network guidelines and have a balanced discussion with the patient weighing the potential progression-free survival benefits with the potential effect of additional therapy on quality of life. After completion of frontline chemotherapy, surveillance strategies frequently include a combination of clinical evaluation strategies, such as pelvic examinations, imaging when indicated, and CA 125 monitoring.<sup>69</sup> Although many women do prefer to have CA 125 levels monitored during their surveillance periods, early identification of recurrence by a rising CA 125 has not been associated with an improvement in progression-free or overall survival,<sup>70</sup> and therefore may be reasonably excluded from routine monitoring if not desired by the patient.

During the COVID-19 pandemic, risk-benefit ratios have influenced the decision to proceed to surgery and the selection of chemotherapy. More women are being treated with neoadjuvant chemotherapy in lieu of radical debulking efforts that are more likely to result in a transient intensive care unit admission postoperatively. The number of neoadjuvant chemotherapy cycles also increased for many women in an effort to postpone surgical debulking until resources were less constrained. Decisions on maintenance bevacizumab have become more complex—oncologists are having to decide whether the potential improvement in progression-free survival is worth the risks associated with increased contact with

the health care system. Physicians may favor less common oral regimens over more frequently used intravenous regimens, particularly in settings where superiority of one regimen over the other has not been demonstrated. Telemedicine utilization rapidly increased, and surveillance visits have been postponed. Many clinical trials were on hold, and those that remained open had to adjust to the changing climate of clinical care, with many studies accepting protocol deviations. As is the case throughout the health care system, we anticipate that some of the changes initiated by the COVID-19 pandemic will remain and some will revert to previous practices. Still, we believe that an in-person visit including a clinical examination will allow oncologists to most effectively counsel patients on the best options available to them. These studies on how COVID-19 has affected our clinical practice and our patients' outcomes and the general knowledge gained during this pandemic should provide a framework for future treatment algorithms during a pandemic.

## GENETIC TESTING FOR WOMEN WITH OVARIAN CANCER

The Society of Gynecologic Oncology, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network currently recommend that all women with a new diagnosis of epithelial ovarian cancer be offered genetic testing.<sup>71–73</sup> At the time of diagnosis, we also suggest performing a three-generation pedigree. Studies demonstrate that approximately 10–20% of ovarian cancers are related to germline mutations.<sup>7,74,75</sup> Additionally, a Committee Opinion by the American College of Obstetricians and Gynecologists recommends that cascade testing be performed; ie, that relatives of women with known genetic mutations should be offered genetic testing.<sup>76</sup> In support of this strategy, a cost effectiveness analysis showed that genetic testing for *BRCA1*, *BRCA2*, and *PALB2* for all patients with breast cancer is cost effective. Furthermore, this strategy could prevent more deaths than testing only for *BRCA1* and *BRCA2*, or testing only patients with breast cancer who meet family history or clinical criteria.<sup>77</sup> However, despite these anticipated benefits, a recent study indicates that genetic testing for women diagnosed with ovarian, fallopian tube, or primary peritoneal cancers is underused.<sup>78</sup> Rates of cascade testing have been similarly disappointing. A survey of individuals who carry a mutation in a cancer gene, such as *BRCA*, showed that, after disclosing their results to their family members, only 30% of all at-risk first-degree family members underwent genetic

testing.<sup>79</sup> Moreover, there is no consensus on who should perform the genetic testing or the best method for genetic counseling,<sup>80–82</sup> although studies seeking to establish best practices are ongoing.<sup>83</sup>

Regardless, there is no doubt all patients with breast and ovarian cancer should be genetically tested, and that the access of their family members to testing should be increased. Because frontline treatment indications now include poly (ADP-ribose) polymerase inhibitor maintenance therapy for women with *BRCA* mutations, it is clear that genetic testing should be performed close to the time of diagnosis. We recommend performing genetic counseling and testing for all patients with epithelial ovarian cancer as early in their disease course as possible.

## CONCLUSION

Recent advances in ovarian cancer research have expanded options for patients with ovarian cancer in 2020, but these same advances have also made decision making more complicated for physicians. Many questions remain and we expect the landscape to continue to shift and therapeutic options and treatment algorithms to become more complex. The COVID-19 pandemic has only added to the current complexity as practical considerations of in-person visits, intensive care unit bed availability, and patient concerns also factor into treatment decisions. Over the past 2 years we have made significant progress and early data suggest that poly (ADP-ribose) polymerase inhibitor might improve overall survival and occasionally cure advanced disease.<sup>84</sup> Moreover, we know that patients treated by gynecologic oncologists at centers with high surgical volume and high rates of macroscopically complete resections have better survival outcomes.<sup>11</sup> We also know that we must underline the importance of quality-of-life considerations and that we should continue to encourage women to participate in clinical trials to take advantage of and help develop future therapy strategies. Through ongoing advances, we hope that ovarian cancer will transition from a historically highly fatal disease to a chronic but treatable illness, and, increasingly, to one that is curable.

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