Wanna Get Away? Maintenance Treatments and Chemotherapy Holidays in Gynecologic Cancers

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overview

Epithelial ovarian cancer has a very high rate of relapse after primary therapy; historically approximately 70% of patients with a complete clinical response to surgery and adjuvant chemotherapy will relapse and die of the disease. Although this number has slowly improved, cure rates remain less than 50%. As such, maintenance therapy with the aim of preventing or delaying disease relapse and the goal of improving overall survival has been the subject of intense study. Numerous earlier studies with agents ranging from radioactive phosphorus to extended frontline therapy or to monthly taxol administration demonstrated encouraging improvements in progression-free survival (PFS) only to find, disappointingly, no benefit in overall survival. In addition, the PFS advantage of maintenance therapy was associated with disconcerting side effects such that maintenance therapy was not adapted as standard of care. Studies with bevacizumab and PARP inhibitors have demonstrated a PFS advantage with a manageable side-effect profile. However, an overall survival advantage remains unclear, and the use of these approaches thus remains controversial. Furthermore, in recurrent disease, the length of chemotherapy and benefits of extended chemotherapy is unclear. Thus, additional trials assessing maintenance strategies in ovarian and other gynecologic malignancies are needed.

MAINTENANCE STRATEGIES IN GYNECOLOGIC CANCERS, TRIAL DESIGN, AND ENDPOINTS

The optimal duration of treatment with chemotherapy, targeted agents, or maintenance strategies in gynecologic malignancies remains to be determined in some settings. Contemporary maintenance strategies can incorporate either a new agent (switch maintenance) or maintain a component of the initial treatment following the standard duration (continuation maintenance).[1-7] Maintenance strategies are typically restricted to patients who achieve a partial response (PR), complete response (CR), or at least stable disease following initial treatment.

As illustrated in Fig. 1, two different trial designs have been used to assess maintenance therapy in gynecologic cancers. The switch-maintenance trial design incorporates the investigational drug versus placebo at the end of standard chemotherapy. This scenario thus selects only those patients who respond to standard-of-care therapy.[5,6,8,9] Recent studies with PARP inhibitors are good examples of this study design in epithelial ovarian cancer (EOC). The other primary approach, called continuation maintenance, includes the maintenance agent in the primary treatment. Trials assessing bevacizumab in EOC incorporated bevacizumab into the induction chemotherapy phase followed by maintenance bevacizumab.[10-13] When bevacizumab was examined in cervical cancer, it was incorporated into initial chemotherapy until progression, unacceptable toxicity, or CR and did not incorporate a maintenance strategy with the drug as part of the study.[14]

The current gold standards for assessing efficacy of novel agents are overall survival (OS) and quality of life (QOL), but PFS has been used to argue for drug use and approval.[1,15] Different QOL assessments have been incorporated into maintenance clinical trials in gynecologic cancers, including the European Quality of Life–5 Dimensions tool, which measures a patient's perceived health state in five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[16] The Functional Assessment of Chronic Illness Therapy (FACIT) tool has specific cancer site–adjusted questionnaires and also includes assessments of physical, social/family, emotional, and functional well-being.[17-19] In fact, changes in FACIT scores from baseline can be measured through the Trial Outcome Index (TOI) score.[17] Other useful QOL assessments that have been incorporated into maintenance trials are quality-adjusted PFS and time without symptoms and toxicity[9]; however, difficulties in effectively assessing QOL and the feasibility of recording OS (larger sample and longer follow-up) led to the incorporation of other time-to-event endpoints (Fig. 2) as follows.

First, PFS is extensively used as the primary endpoint in maintenance trials in gynecologic cancers.[5,8,20] One

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Accepted on May 17, 2019 and published at ascopubs.org on May 17, 2019: DOI https://doi.org/10.1200/EDBK_238755

PRACTICAL APPLICATIONS

- The data support the use of maintenance olaparib in those with a mutation (somatic or germline) in *BRCA1/2*. Somatic and germline *BRCA1/2* testing needs to be incorporated from the initial clinic visit in order to have this information at the appropriate time.
- For women with advanced ovarian cancer, particularly those with stage IV, bevacizumab as maintenance treatment has shown to improve progression-free survival (PFS), as well as overall survival (OS) in high risk-patients, and should be considered.
- Women with *BRCA* mutations who achieve a partial or complete response to first-line therapy should be treated with PARP inhibitor maintenance therapy with olaparib (SOLO1).
- For women with recurrent ovarian cancer who respond to repeat treatment with a platinum-based regimen, maintenance treatment with a PARP inhibitor consistently improves PFS compared to no maintenance treatment. This benefit was seen in this population regardless of *BRCA1/2* mutation status.
- For women with recurrent or metastatic cervical cancer, chemotherapy plus bevacizumab is associated with an improvement in overall survival compared to chemotherapy alone. For those who discontinue chemotherapy, continuation of bevacizumab remains a reasonable strategy.

of the benefits of using PFS is the lack of confounding by subsequent lines of treatment, and PFS is often used as a surrogate of OS in EOC.[21] It is important to note that the association of PFS with OS in the contemporary oncology era must be done with caution, as most published literature outside of colorectal cancer and EOC has not supported this surrogacy.[15]

Second, although subsequent increasingly toxic therapy may be delayed, a PFS improvement does not always correlate with an improved QOL because treatment-related toxicity and convenience must be kept in mind.[1,15] In fact, PFS should not be used as the main endpoint for the approval of a new treatment if clinical benefit is not demonstrated.[1] The American Society of Clinical Oncology Value Framework and the European Society of Medical Oncology Magnitude of Clinical Benefit Scale are validated tools that stratify the magnitude of clinical benefit of new drugs and help physicians deliver cost-effective cancer care.[22,23] In the recurrent ovarian cancer setting, the Fifth Ovarian Cancer Consensus Conference established that PFS must be

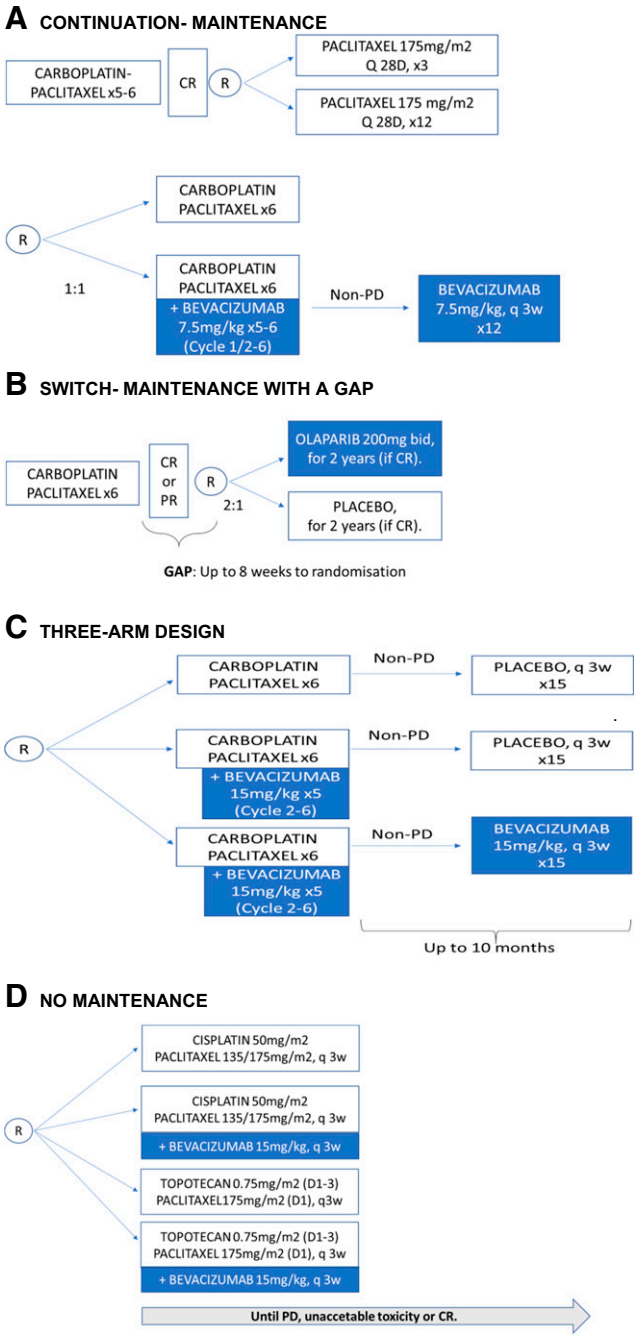

FIGURE 1. Trial Designs Used to Assess Maintenance Therapy in Gynecologic Cancers

(A) Continuation maintenance. (B) Switch maintenance: maintenance with a gap. (C) Three-arm design. (D) No maintenance.
Abbreviations: CR, complete response; R, randomized; PD, progressive disease; PR, partial response.
Adapted from Markman et al[2] (A), Moore et al[8] (B), Burger et al[12] (C), and Tewari[14] et al (D).

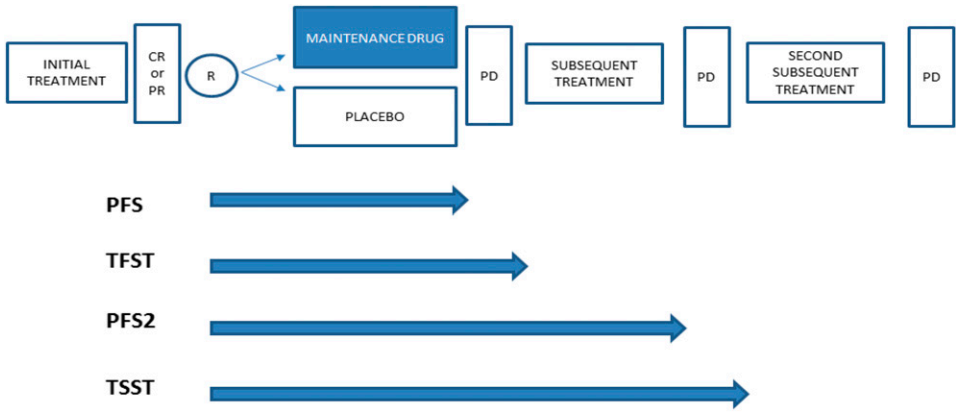

FIGURE 2. Time-to-Event Endpoints
Abbreviations: CR, complete response; PR, partial response; R, randomized; PD, progressive disease; PFS, progression-free survival; TFST, time to first subsequent therapy or death; PFS2, progression while receiving second-line therapy; TSST, time to second subsequent therapy or death.

supported by clinical benefit.[24] It was also agreed that OS is the preferred endpoint when median OS is expected to be less than 12 months, whereas PFS supported by additional measurements of clinical benefit is the preferred endpoint when median OS is more than 12 months.

Third, time from the patient's random assignment to progression while receiving second-line therapy (PFS2) or death may be a better surrogate of the effect of maintenance treatment, because it reflects disease control and maintenance effects in subsequent lines.[1]

Finally, time to first subsequent therapy (TFST) or death and time to second subsequent therapy or death (TSST) assess the time from study treatment randomization to the start date of the first and second subsequent anticancer therapies, respectively. TSST can also be approximated to PFS2, and it is especially useful when regular tumor assessment until the time of second progression is not feasible.[1]

Cost-effectiveness analysis provides a standard technique to estimate the cost relative to health gains of a new intervention, such as the incorporation of a maintenance treatment.[25] One approach to addressing this question is the incremental cost-effectiveness ratio, which calculates the ratio of the costs to the effectiveness of two medical interventions and is expressed as cost per unit of the measure of effect (where cost is expressed in terms of monetary units and effects can be measured in terms of health status or another outcome of interest).[25] Although no formal willingness-to-pay threshold is currently used for health in the United States, $100,000 to $150,000 USD per quality-adjusted life-year is used as a reference.[26] Besides clinical benefit, treatment-related toxicity, and QOL impact, cost-effectiveness must be recognized as an important factor by regulatory agencies to select the appropriate treatment strategies.[7]

OVARIAN CANCER

Approximately 90% of all ovarian cancers are epithelial and can be divided into five distinct histologic subtypes: high-grade serous ovarian cancer (HGSOC), low-grade serous ovarian cancer (LGSOC), endometriod, clear cell, and muscinous ovarian cancers.[27,28] Of these, approximately 70% are the HGSOC histologic type and are diagnosed in advanced stages (III/IV).[27,28] Maintenance trials assessing PARP inhibitors have predominantly included patients with HGSOC (a small number of patients with high-grade endometrioid cancer were also included),[5,6,9,29] whereas most EOC subtypes are included in trials assessing bevacizumab (carcinosarcoma was excluded in ICON7).[11,13] Although the histologic subtype of ovarian cancer should be considered as a stratification criterion for clinical trials, this remains a challenge in treatment access in rare cancer subtypes.[24]

The Role of Consolidation/Maintenance Therapy Following Adjuvant Therapy

Phase III trials comparing adjuvant treatment with either carboplatin/paclitaxel or cisplatin/paclitaxel following debulking surgery have incorporated six cycles of treatment.[30,31] The administration of six cycles of chemotherapy with carboplatin and paclitaxel has become standard practice for women with advanced ovarian cancer, although some trials have suggested that fewer cycles might be just as effective.[32-34] Three randomized trials compared five to six cycles with eight, 10, and 12 cycles, showing no benefit of continuation of the treatment beyond five or six cycles.[35] As discussed below, several strategies have been explored following frontline chemotherapy treatment, including consolidation or maintenance chemotherapy, antiangiogenics, and PARP inhibitors. The role of maintenance immune-checkpoint inhibitors alone or in combination is currently being explored in clinical trials (NCT02718417).

Compared with hematologic malignancies, the role of maintenance or consolidation chemotherapy in ovarian cancer is limited because no survival advantage has been found with this strategy to date.[36] The first trial to demonstrate an improvement in PFS with maintenance chemotherapy was the SWOG-9701/GOG-178 phase III study of either three or 12 cycles of single-agent paclitaxel

administered every 28 days to patients who had achieved a CR to primary platinum/paclitaxel-based chemotherapy.[2] In an updated analysis, the median PFS was 22 months with 12 cycles versus 14 months with three cycles (p = .006), but there remained no difference in OS (53 vs. 48 months, p = .34).[3] A more recent phase III study (GOG-212, NCT00108745) evaluated a year of monthly maintenance chemotherapy with paclitaxel, the paclitaxel conjugate CT-2103, or observation after CR to primary cytotoxic chemotherapy. The study findings showed a 5.5-month prolongation of PFS with paclitaxel treatment versus observation but no improvement in OS.[37] A Cochrane Collaboration meta-analysis of eight randomized trials in which maintenance chemotherapy, with either cisplatin, anthracyclines, paclitaxel, or the combination of cisplatin and doxorubicin, given following remission showed no evidence of improvement in OS or PFS.[38] The extended chemotherapy was associated with an increased risk of cumulative toxicity.[38]

First-line maintenance antiangiogenics Bevacizumab, a humanized anti-VEGF monoclonal antibody, was the first drug licensed for maintenance therapy in ovarian cancer. Two trials have shown notable improvement in PFS when bevacizumab is given with first-line carboplatin and paclitaxel chemotherapy and then continued as maintenance therapy (Fig. 1).[11,12] An OS advantage for bevacizumab has been seen but may be restricted to patients with stage IV disease.

In ICON7 (NCT00483782), patients with histologically confirmed, high-risk, early (International Federation of Gynecology and Obstetrics [FIGO] stage I or IIA with clear cell or grade 3 tumors) or advanced-stage (FIGO stage IIB to IV) EOC (n = 1,528) were randomly assigned to receive standard carboplatin and paclitaxel chemotherapy or to the same regimen plus bevacizumab (7.5 mg/kg), given concurrently every 3 weeks for five or six cycles and continued monthly for 12 additional maintenance cycles or until disease progression occurred in the bevacizumab group.[11] In the GOG-0218 study (NCT00262847), treatment-naïve patients with incompletely resectable stage III or any stage IV EOC (n = 1,873) were randomly assigned (1:1:1) to carboplatin plus paclitaxel without bevacizumab (15 mg/kg), carboplatin plus paclitaxel with bevacizumab for up to six cycles, or carboplatin plus paclitaxel with bevacizumab for six cycles followed by single-agent bevacizumab for up to 15 additional doses.[12] There were notable population differences in both studies. Whereas ICON7 included patients with early-stage high-risk cancer, GOG-0218 only included patients with stage III to IV disease. Moreover, patients were included in ICON7 regardless of the presence of residual disease in initial surgery, whereas only those patients with incompletely resected disease were eligible for inclusion in GOG-0218 (there was a protocol amendment to allow inclusion of patients with stage III residual disease of < 1 cm). Both studies showed that administration of bevacizumab during and following primary chemotherapy offered a modest benefit in PFS of 2 months in ICON7 (hazard ratio [HR], 0.93; p = .25) and 4 months in GOG-0218 (HR 0.72; p < .001).[11,12,39]

In ICON7, no OS benefit of bevacizumab was recorded (median OS of 58.6 vs. 58 months in the standard chemotherapy group vs. the bevacizumab group; HR 0.99; 95% CI, 0.85–1.14; p = .85).[39] A predefined subgroup analysis of 502 patients with poor prognosis disease (FIGO stage III with residuum > 1 cm, any FIGO stage IV, or no debulking surgery) showed a significant difference in OS between women who received bevacizumab plus chemotherapy and those who received chemotherapy alone (median OS of 30.2 months with standard chemotherapy vs. 39.7 months with bevacizumab; HR 0.78; 95% CI, 0.63–0.97, p = .03).[39] Additional analysis has shown a PFS benefit from bevacizumab in all subgroups explored, which was greatest in the high-risk group (HR 0.73; p = .001).[39,40]

In the GOG-0218 study, the estimated median PFS was 10.3 months for patients receiving chemotherapy without bevacizumab compared with 14.1 months for patients receiving bevacizumab with chemotherapy followed by single-agent bevacizumab (HR 0.72; 95% CI, 0.62–0.82; p < .001).[12] In an analysis where patients with increased CA125 levels were censored (as requested by regulatory authorities), PFS was 12 months in the control group and 18 months in the maintenance bevacizumab arm (HR 0.64; p < .001).[12] As reported by Burger et al,[41] no differences in OS were found in the overall population (HR 0.96; 95% CI, 0.85–1.09; p = .53) but final publication of the study results is awaited.[12,41] For patients with stage IV disease, median OS was 32.6 months in the chemotherapy arm and 42.8 months in the maintenance bevacizumab arm (HR 0.774; p value not reported).

Figure 3 illustrates bevacizumab approval by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). Given the potential impact of bevacizumab on OS, it is important to also know the drug's effects on QOL. In ICON7, the mean global QOL score at 54 weeks was higher in the standard chemotherapy group than in the bevacizumab group (mean ± SD of 76.1 ± 18.2 vs. 69.7 ± 19.1 points; difference, 6.4 points; 95% CI, 3.7–9.0, p < .0001).[42] However, in GOG-0218, bevacizumab compromised QOL, as measured by the TOI score, to a mild extent during chemotherapy but had no prolonged effect after chemotherapy completion.[12] GOG-0218 participants received bevacizumab or placebo every 3 weeks, whereas no placebo was given in ICON7. The reduction in QOL during maintenance bevacizumab seen in ICON7 and not observed in GOG-0218 may be attributable to patient attendance for infusions every 3 weeks in the bevacizumab and placebo arms in GOG-0218, rather than only in the bevacizumab arm as in ICON7. The observation that

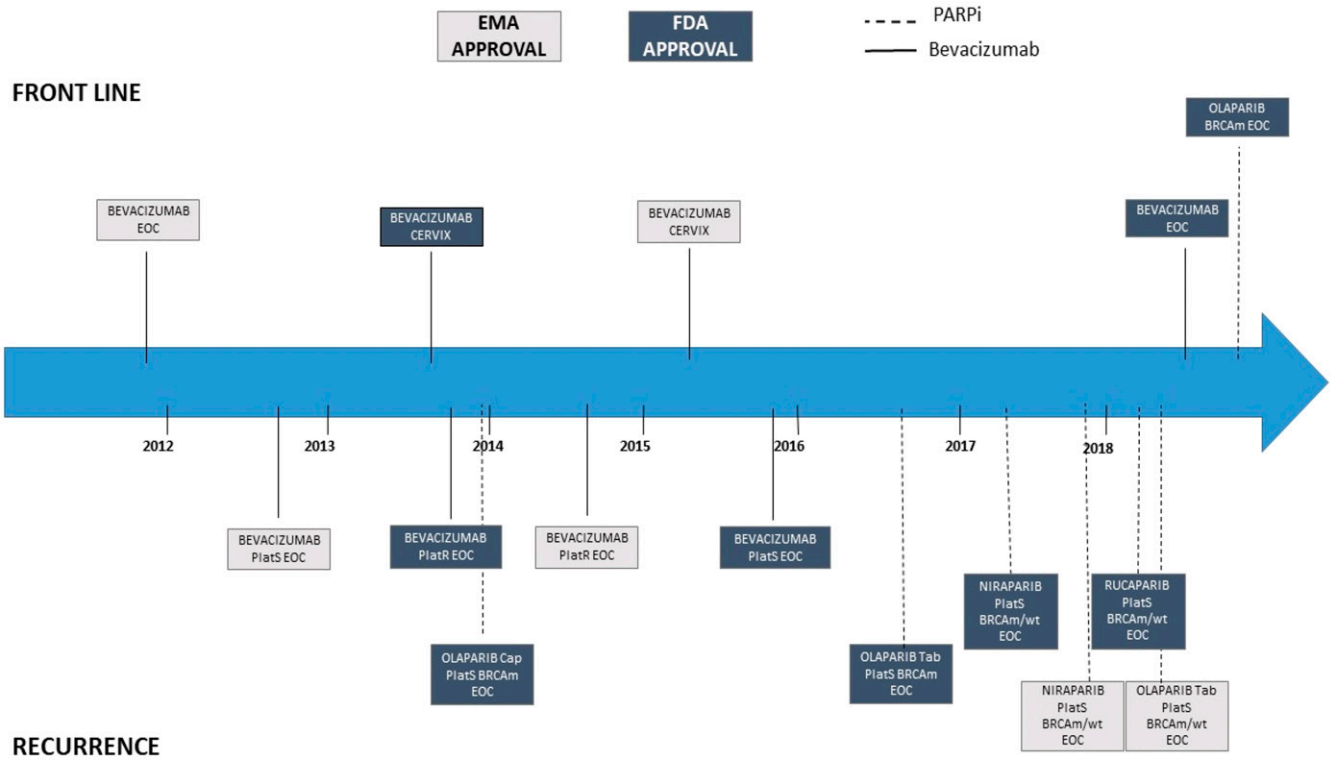

FIGURE 3. Drugs Approved by the European Medicines Agency and U.S. Food and Drug Administration for Treatment of Gynecologic Cancers
Abbreviations: EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; PARPi, PARP inhibitor; EOC, epithelial ovarian cancer; PlatS, platinum sensitive; PlatR, platinum resistant.

GOG-0218 participants showed no deterioration in QOL during maintenance bevacizumab suggests that toxicity of maintenance bevacizumab has minimal impact on QOL.[12] Unlike chemotherapy and PARP inhibitors, the majority of patients receiving bevacizumab have minimal symptomatic side effects.[43,44] Pain is one of the more common therapy-related symptoms for patients taking bevacizumab than placebo; for many patients, this is manifested as joint or muscle pain. Gastrointestinal perforation/fistula is a rare but serious adverse event for patients with advanced disease involving the bowel.[44]

Two oral antiangiogenic agents have shown significant improvement in PFS as maintenance therapy with no OS advantage. First-line maintenance treatment with pazopanib showed an improvement in PFS (17.9 vs. 12.3 months; HR 0.77; 95% CI, 0.64–0.91; p = .002), with a 33% treatment discontinuation rate attributable to toxicity.[45] Although a category IIb recommendation in the National Comprehensive Cancer Network Guidelines, this has not been licensed for use in ovarian cancer. Frontline nintedanib improved PFS by less than 1 month (17.2 vs. 16.6 months; HR 0.84; 95% CI, 0.72–0.98; p = .024) and is not marketed.[46]

Paclitaxel administered weekly has a potential antiangiogenic effect.[47] In the GOG-262 trial (NCT01167712), patients who received weekly paclitaxel plus 3-weekly carboplatin but not bevacizumab had a 3.9-month improvement in PFS compared with those who received 3-weekly chemotherapy. However, there was no improvement in PFS in the weekly arm if bevacizumab was given to both arms.[48] Dose-dense paclitaxel administration (without bevacizumab) showed a PFS and OS benefit in a Japanese population.[49] However, no benefit of this approach was found in European trials, possibly owing to pharmacogenomic influences. When weekly paclitaxel and 3-weekly carboplatin was compared with standard 3-weekly chemotherapy in the ICON-8 study (NCT01654146), no differences in PFS were found (17.9 vs. 20.6 months in the 3-weekly arm vs. the weekly paclitaxel arm; HR 0.92; p = .45).[50] In the MITO7 trial, carboplatin and paclitaxel were both administered weekly, with a lower-dose intensity of paclitaxel, and showed no differences in PFS compared with the 3-weekly regimen (17.3 vs. 18.3 months for 3-weekly treatment vs. the weekly regimen; HR 0.96; 95% CI, 0.8–1.16; p = .66).[51] The suggestion that administering frontline weekly paclitaxel is equivalent to adding bevacizumab has not been proven.

Maintenance PARP inhibitors The randomized phase III SOLO1 trial (NCT01844986) assessed maintenance olaparib/placebo treatment following first-line platinum-based chemotherapy without bevacizumab.[8] Eligible patients had

stage III and IV HGSOC or endometrioid ovarian cancer with germline or somatic *BRCA*m (g/s*BRCA*m) and a PR or CR to frontline chemotherapy. Most of the women had germline *BRCA*m (g*BRCA*m) and a CR to frontline treatment. Patients who had no evidence of disease stopped treatment after 2 years of treatment completion. The primary trial endpoint was PFS assessed by the investigator. The risk of disease progression at 3 years was significantly lower in the olaparib arm compared with placebo (rate of freedom from disease of 60% vs. 27% in the olaparib arm vs. the placebo arm; HR 0.3; 95% CI, 0.23–0.41; $p < .001$).[8] PFS2 at 3 years was also significantly better in the olaparib arm (rate of freedom from PFS2 of 75% vs. 60% in the olaparib arm vs. the placebo arm; HR 0.50; 95% CI, 0.35–0.72; $p < .001$). The OS data are still immature (21% of maturity), but no significant differences have been found thus far (HR 0.95; 95% CI, 0.6–1.53). Serious adverse events were considered manageable and occurred for 22% of patients in the olaparib arm and 12% in the placebo arm, with anemia being the most commonly reported. As reported in other PARP inhibitor studies, acute myeloid leukemia occurred for 1% of the patients receiving olaparib.[8] QOL was assessed with the ovarian cancer–specific FACT (Functional Assessment of Cancer Therapy) questionnaire. The QOL TOI score remained stable in the olaparib arm and decreased in the placebo arm (group difference in change, –3 points; 95% CI, –4.78 to –1.22) but was not considered clinically meaningful.[8]

PFS and PFS2 results are outstanding for the advanced ovarian cancer setting; however, QOL differences are not clinically notable and long-term analysis is warranted to explore the impact of frontline PARP inhibitor maintenance on OS for *BRCA1/2*m carriers. Cost-effectiveness analysis is also pending. Frontline maintenance olaparib treatment was approved by the FDA in December 2018 for *BRCA*m carriers (Fig. 3).

Platinum-Sensitive Recurrence

Antiangiogenics In the OCEANS trial (NCT00434642), patients with platinum-sensitive recurrent EOC and measurable disease were randomly assigned to carboplatin and gemcitabine in combination with bevacizumab/placebo for six to 10 cycles, followed by maintenance bevacizumab/placebo until disease progression or unacceptable toxicity.[13,52] The bevacizumab arm showed PFS benefit compared with placebo (12.4 vs. 8.4 months; HR 0.484; 95% CI, 0.388–0.605; $p < .0001$). There were no notable differences in OS.[13,52] The GOG-0213 phase III trial (NCT00565851) confirmed benefit of bevacizumab in combination with carboplatin and paclitaxel among platinum-sensitive patients, with a trend toward OS benefit (HR 0.829; $p = .056$).[53]

Cediranib, an oral pan-VEGF receptor tyrosine kinase inhibitor given as maintenance therapy, improved PFS by 2.3 months for patients with relapsed disease (8.7 vs. 11 months; HR 0.56; $p < .0001$), with a nonsignificant improvement in OS (19.9 vs. 27.3 months; HR 0.85; $p = .21$).[54,55] Cediranib is not marketed but is undergoing trials in combination with olaparib.

Retreatment with bevacizumab in the first platinum-sensitive relapse setting after progression to frontline bevacizumab maintenance showed PFS benefit (8.8 vs. 11.8 months; HR 0.51; $p < .001$) but not OS benefit (HR 1; $p = .98$).[56] Treatment-related toxicity was as expected and included reports of grade 3 hypertension or greater (27.5% vs. 9.7%; $p < .001$) and proteinuria (4% vs. 0%, $p = .007$), which were more frequent in the bevacizumab arm.

PARP inhibitors Study 19 (NCT00753545) is a pivotal registration randomized phase II trial assessing the switch-maintenance strategy with olaparib/placebo for patients with HGSOC treated with at least two prior lines of platinum-based chemotherapy and response to the last treatment. The primary study endpoint was PFS, which was significantly longer in the olaparib arm than in the placebo arm (8.4 vs. 4.8 months; HR 0.35; 95% CI, 0.25–0.49; $p < .001$).[57] Although the trial was not powered to assess OS, no statistically significant differences were found (HR 0.73; 95% CI, 0.55–0.96; $p = .025$; required threshold, $p < .0095$).[58] A preplanned retrospective analysis of the data by *BRCA*m status showed that 51% of patients harbored a g/s*BRCA*m.[29] An exploratory analysis demonstrated a longer PFS in *BRCA*m carriers (HR 0.18; $p < .0001$), pointing out *BRCA*m as a response biomarker. Regarding QOL, no notable changes in TOI, FACT–Ovarian Cancer, or FACT–Ovarian Cancer Symptom Index questionnaire scores were found.[57]

A randomized open-label phase II trial, Study 41 (NCT01081951), assessed the effect of olaparib as a continuous-maintenance strategy in platinum-sensitive recurrent HGSOC, with or without *BRCA*m.[59] Patients were randomly assigned to receive olaparib in combination with carboplatin and paclitaxel followed by maintenance olaparib, or carboplatin and paclitaxel alone. Women receiving olaparib had an improvement in PFS of 12.2 months in the combination arm compared with 9.6 months PFS in the chemotherapy-only arm (HR 0.51; 95% CI, 0.34–0.77; $p = .012$), with the greatest benefit seen for *BRCA*m carriers. Although the study was not designed to measure the contribution of each treatment, the late separation of the PFS curves suggested that improvement was mainly attributable to the maintenance phase. The treatment was well tolerated, and adverse events were 10% more common in the combination phase in the olaparib arm.[59]

The randomized phase III SOLO2/ENGOT-Ov21 trial (NCT01874353) assessed olaparib/placebo as a switch-maintenance treatment for patients with platinum-sensitive HGSOC or endometrioid ovarian cancer with

g*BRCA*m.[9] The primary study endpoint was investigator-assessed PFS, which was significantly longer in the olaparib arm (19.1 vs. 5.5 months; HR 0.3; 95% CI, 0.22–0.41; $p < .0001$). PFS2 (HR 0.5; $p < .0002$), time to first subsequent therapy or death (HR 0.28; $p < .0001$), and TSST (HR 0.37; $p < .0001$) also favored the olaparib arm. OS data were still immature but again showed no significant difference (HR 0.8; $p = .43$). Similarly, regarding QOL, there were no significant differences in TOI scores.

The randomized phase III ENGOT-OV16/NOVA trial (NCT01847274) assessed niraparib/placebo switch maintenance for women with platinum-sensitive recurrent HGSOC or ovarian cancer with *BRCA*m and response to the last platinum-based chemotherapy.[5] The study included two independent cohorts, patients with g*BRCA*m (37%) and those without g*BRCA*m. Homologous recombination deficiency (HRD) was assessed with the Myriad myChoice HRD test (Myriad Genetics, Salt Lake City, UT). PFS was significantly longer in the niraparib arm versus the placebo arm in all prespecified cohorts, including the g*BRCAm* cohort (21 vs. 5.5 months; HR 0.27; 95% CI, 0.17–0.41; $p < .001$), the nongermline *BRCAm* cohort with HRD (12.9 vs. 3.8 months; HR 0.38; 95% CI, 0.24–0.59; $p < .001$), and the g*BRCA* wild-type cohort (9.3 vs. 3.9 months; HR 0.45; 95% CI, 0.34–0.61; $p < .001$).[5] Preliminary data showed a benefit in PFS2 in the g*BRCA*m (HR 0.48; $p = .006$) and nongermline *BRCA*m (HR 0.69; $p = .03$) cohorts. OS and TSST data have not yet been reported.[5] Adverse events and PFS were similar among patients older than age 70.[60] QOL was assessed through the FACT–Ovarian Cancer Symptom Index and European Quality of Life–5 Dimensions questionnaires but did not show any notable differences across the two groups.[61]

The randomized phase III ARIEL3 trial (NCT01968213) assessed rucaparib/placebo maintenance therapy in platinum-sensitive, HGSOC, or endometrioid ovarian cancer with response to the last treatment. Loss of heterozygosity was used as a marker of HRD through the Foundation Medicine T5 NGS tool (Foundation Medicine, Cambridge, MA). Patients in the rucaparib arm demonstrated an increase in PFS in all prespecified subgroups compared with placebo, including g/s*BRCA1/2m* carriers (16.6 vs. 5.4 months; HR 0.23; 95% CI, 0.16–0.34; $p < .0001$), patients with HRD (13.6 vs. 5.4 months; HR 0.32; 95% CI, 0.24–0.42; $p < .0001$), and the intention-to-treat population (10.8 vs. 5.4 months; HR 0.36; 95% CI, 0.30–0.45; $p < .0001$).[6] In this study, PFS2 and TSST have not yet been analyzed and patient-reported outcomes have not been published.

Although there is a PFS benefit associated with maintenance PARP inhibitors in platinum-sensitive recurrence, OS benefit remains to be defined.[43] Figure 3 illustrates EMA and FDA approvals of PARP inhibitors for use in treating EOC.[62-67]

Unlike non–small cell lung cancer trials in which EGFR inhibitors were initially given to a large population and subsequent studies were able to determine the biomarker of response,[68] initial ovarian cancer trials assessing PARP inhibitors were initially restricted to women with *BRCA1/2*m and the target population has subsequently been expanding. In fact, the NOVA (NCT01847274) and ARIEL3 (NCT01968213) trials incorporated an assay to define patients with HRD, but these studies were unable to accurately predict who would benefit from treatment.[5,6] Currently, the FDA and EMA are not restricting access to maintenance PARP inhibitors to *BRCA*m or HRD carriers.[64,65]

Optimal treatment following PARP inhibitor maintenance, retreatment with PARP inhibitors, and new combinations with antiangiogenics are under investigation (e-VOLVE, NCT02340611).[69] In fact, several mechanisms of resistance to PARP inhibitors have been reported, including *BRCA* reversion mutations, nonhomologous end-joint repair alterations, and mutations in genes that encode shieldin subunits.[70-72]

Platinum-Resistant Recurrence

Antiangiogenics In the AURELIA trial (NCT00976911), patients with platinum-resistant disease were randomly assigned to either chemotherapy alone (pegylated liposomal doxorubicin, topotecan, or weekly paclitaxel) or chemotherapy combined with 10 mg/kg^2 of bevacizumab weekly or 15 mg/kg every 3 weeks until progression or unacceptable toxicity.[20] The median PFS was 6.7 months in the combination arm compared with 3.4 months in the chemotherapy-alone arm. Although no notable survival advantage was detected, this could be because 40% of patients receiving chemotherapy alone crossed over to receive bevacizumab on progression. The median duration of therapy was three cycles in the chemotherapy-alone arm versus six cycles in the combined arm. In an exploratory analysis, the benefit was most pronounced in the weekly paclitaxel cohort.[10] More than 20% of AURELIA patients were still receiving therapy after 10 cycles.

As illustrated in Table 1, a Belgian analysis showed that bevacizumab was more cost-effective when given first line than when given at relapse.[73] Selecting patients with the worse prognosis in both the GOG128 and ICON7 trials improved the cost-effectiveness.

Intermittent treatment or chemotherapy holidays Paclitaxel is one of the most active nonplatinum drugs used in monotherapy or in combination with bevacizumab in recurrent platinum-resistant EOC.[20,74,75] Although paclitaxel can be administered every 3 weeks or weekly, the dose-dense

TABLE 1. Comparison of Reported Cost-effectiveness by Trial Assessing Bevacizumab

	GOG0128	GOG0128 (Stage 4)	ICON7	ICON7 High Risk	OCEANS	AURELIA
Mean duration of bevacizumab treatment, weeks	41.93	35.7	42.99	NR	50.74	26.2
Mean OS HR	0.885	0.72	0.990	0.780	0.960	0.850
ICER (€/QALY gained)	157,816	51,931	443,027	82,277	587,182	172,370

Abbreviations: NR, not reported; OS, overall survival; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

weekly regimen is the most established in platinum-resistant disease. There is a potential antiangiogenic effect with the weekly regimen, although the mechanism is still unknown.[47] A Swedish randomized trial assessed paclitaxel monotherapy (weekly vs. every 3 weeks) in recurrent ovarian cancer and failed to note any outcome differences between the two administration types.[76] The 3-weekly regimen was associated with increased hematologic toxicity, arthralgia/myalgia, and neuropathy, whereas the weekly regimen had significantly increased nail toxicity. Different durations and schedules of weekly paclitaxel have been incorporated in clinical trials in recurrent disease. For example, in the AURELIA trial (NCT00976911), weekly paclitaxel was administered until disease progression or unacceptable toxicity[20] compared with topotecan, which was administered until progression or for 6 months past the maximal response.[74] Furthermore, in a GOG phase II trial (NCT00003160), patients could be switched to a schedule of 3 weeks on and 1 week off following the administration of 12 weeks of paclitaxel administered weekly with no break.[75]

The dose-dense regimen can be less convenient for the patient, with weekly clinic visits. Both schedules are associated with cumulative toxicity, including neurotoxicity, which is the main cause of cancer disability.[77] As a result, treatment holidays or treatment-free periods have been introduced; however, preclinical data suggest that longer taxane-free intervals might be associated with treatment resistance.[78,79] Ovarian cancer xenograft models have shown that continuous administration of taxanes is associated with less treatment resistance, including drug resistance–related genes and drug efflux transporter expression, as well as reduced tumor growth and proliferation.[78,79]

Pegylated liposomal doxorubicin has been used as monotherapy or in combination with bevacizumab in platinum-resistant disease.[20,80,81] The duration of pegylated liposomal doxorubicin treatment remains controversial for patients who have had a PR/CR after six cycles of therapy. For example, in the AURELIA trial (NCT00976911), treatment was administered until unacceptable toxicity or progression.[20] Conversely, in a phase III trial comparing pegylated liposomal doxorubicin with topotecan, treatment was administered for up to 12 months or continued further if the patient had sustained clinical benefit.[80] In patients receiving treatment for more than 12 consecutive months, cumulative toxicities can include skin toxicity and mucositis, and must be kept in mind.[20,80,81] Risk of cardiac toxicity with pegylated liposomal doxorubicin in EOC was reported to be low.[82,83]

If patients have had no symptomatic benefit or evidence of response on serial CA125 measurements or scans after two or three cycles, chemotherapy should be stopped. It is clear that if a patient has responded to treatment but is developing therapy-related toxicity, it is sensible to give the patient a rest from the toxic therapy. However, it is unclear whether patients given a rest from therapy after evidence of symptom benefit having received three to six cycles would respond again on reintroduction of the same therapy. Therapy could be reintroduced after an agreed rest period or at first development of symptoms or on CA125 or scan evidence of progression. It is possible that such an approach would be as effective as maintenance therapy with improved QOL. Further studies assessing the effect of treatment-free intervals and their intermittent use are needed in EOC.

Hormonal Treatment

A recent meta-analysis of endocrine therapy in ovarian cancer demonstrated a clinical benefit rate of 41% among 2,490 patients in 53 trials, with a possibly greater effect in low-grade tumors.[84] Tamoxifen marginally appeared to be the most active agent.[84] The only randomized trial conducted among mostly asymptomatic patients with nonmeasurable disease and evidence of biochemical progression following first-line treatment (grades 1 and 2: 32.9%) was between thalidomide and tamoxifen and showed significantly improved OS in the tamoxifen arm (24 vs. 33.2 months for thalidomide vs. tamoxifen; HR 1.76; 95% CI, 1.16–2.68).[85] Because hormonal treatment is well tolerated and inexpensive, it has been considered a reasonable option for women who would prefer some active management as maintenance therapy or for an asymptomatic rise in CA125 levels, over observation only.[86] However, the results are confounded by the inclusion of patients with LGSOC and other histologic subtypes.

LGSOCs are characterized by slow growth, relative chemotherapy resistance, and higher estrogen and progesterone receptor expression.[87,88] A retrospective study showed that the administration of maintenance hormonal

treatment in stage II to IV LGSOC, following debulking surgery and adjuvant chemotherapy, was associated with PFS improvement (26.4 months for observation [95% CI, 21.8–31] vs. 64.9 months for hormonal maintenance [95% CI, 43.5–86.3]; $p < .001$), but no significant differences in OS were found.[89] This study requires prospective validation as well as establishment of the optimal length of adjuvant hormonal therapy.

OTHER GYNECOLOGIC CANCERS

Cervical Cancer

The optimal duration of first-line platinum-based chemotherapy in metastatic or recurrent cervical cancer is still unknown. Several GOG studies have assessed the role of cisplatin combination chemotherapy for six cycles in nonresponders or until disease progression or unacceptable toxicity.[90,91] Four different cisplatin-containing doublets (cisplatin/paclitaxel vs. cisplatin/vinorelbine, cisplatin/gemcitabine, and cisplatin/topotecan) were assessed in the GOG-204 clinical trial (NCT00064077) for a maximum of six cycles in nonresponders (including those with stable disease). Patients with an acceptable toxicity profile and PR were permitted to continue with the treatment after discussion with the study chair.[92] No notable differences were detected with respect to OS when cisplatin/paclitaxel was compared with the three experimental regimens, but there was a trend favoring the cisplatin (50 mg/m^2) and paclitaxel (135 mg/m^2) combination, which emerged as standard of care.[92]

The GOG-240 phase III clinical trial (NCT00803062) assessed cisplatin/paclitaxel or topotecan/paclitaxel with or without 15 mg/kg of bevacizumab through a two-by-two factorial design as first-line treatment in metastatic, persistent, or recurrent cervical carcinoma (Fig. 1).[14] Treatment was administered until disease progression, unacceptable toxicity, or CR. As such, no continuation maintenance with bevacizumab was incorporated as part of this study. A significant improvement in OS (16.8 vs. 13.3 months; HR 0.77; 95% CI, 0.62–0.95; $p = .0068$) and in PFS (8.2 vs. 6 months; HR 0.68; 95% CI, 0.56–0.84; $p = .0002$) favoring the bevacizumab-containing arms was found.[93] Chemotherapy treatments with topotecan-paclitaxel were associated with a significantly higher risk of progression (HR 1.39; 95% CI, 1.09–1.77) but not OS differences.[14] The incidence of fistula was 14.5% in the bevacizumab arm (these patients all received prior pelvic radiotherapy). There were no substantial changes in QOL in the bevacizumab versus nonbevacizumab arms.[14]

Bevacizumab has been the first and only targeted treatment granted approval for use in cervical cancer by regulatory authorities after demonstrating clinically meaningful improvement in OS (Fig. 3).[93] Despite the 3.5-month survival advantage that bevacizumab demonstrated, it is important to discuss potential side effects with patients, such as the risk of fistula, especially for women who have been treated with prior pelvic radiotherapy. Although the number of cycles was restricted to six in nonresponders in initial GOG trials assessing cisplatin combinations, the GOG-240 trial (NCT00803062) did not establish a prefixed number of optimal cycles or a continuation-maintenance strategy with bevacizumab. Given the risk of cumulative toxicity of cisplatin and paclitaxel chemotherapy, including renal impairment and neuropathy, clinicians often must stop the chemotherapy treatment or stop one of the drugs soon after six cycles have been delivered.[77,94,95] The role of bevacizumab as a single-agent maintenance treatment has not yet been explored as part of the GOG-240 clinical trial, and this has led to concerns for regulatory agencies when only single-agent bevacizumab is administered as maintenance treatment.

Endometrial Cancer

Endometrial carcinoma There is substantial heterogeneity within endometrial carcinomas. Although women with low-grade endometrioid endometrial cancer tend to respond to hormonal manipulation, those with high-grade tumors and carcinosarcomas follow a more aggressive course and cytotoxic therapies are recommended.[96,97] To date, no targeted treatment beyond hormonal therapy has been approved for use in endometrial cancer.[97]

Chemotherapy remains the main treatment for advanced endometrial cancer. Doxorubicin, cisplatin, and paclitaxel have been identified as active agents in endometrial cancer.[98] The GOG has completed a series of phase III randomized prospective trials of chemotherapy for advanced-stage or recurrent endometrial carcinoma.[98,99] The GOG177 phase III randomized trial (NCT00698620) compared cisplatin, doxorubicin, and paclitaxel to cisplatin and doxorubicin for a maximum of seven cycles for women with advanced or recurrent endometrial carcinoma. The three-drug regimen was associated with an improved response rate (57% vs. 34%; $p < .01$), longer PFS (8.3 vs. 5.3 months; HR 0.60; $p < .01$), and a slight improvement in OS (15.3 vs. 12.3 months; HR 0.75; $p = .037$) but significantly increased toxicity.[100] The GOG-0209 phase III trial (NCT00063999) compared the cisplatin, doxorubicin, and paclitaxel combination with carboplatin and paclitaxel for seven cycles in a noninferior design. The carboplatin and paclitaxel combination was found to have fewer adverse events and higher compliance and was not less effective than the three-drug regimen.[101] Although both GOG trials incorporated the chemotherapy regimens for seven cycles, six are usually administered in clinical practice.

No maintenance strategies are currently approved for endometrial cancer. A phase II clinical trial assessed bevacizumab in combination with carboplatin and paclitaxel,

followed by maintenance bevacizumab in advanced or recurrent endometrial carcinoma with a maximum of one prior chemotherapy regimen. Only 15 patients were enrolled; five CRs and six PRs were found, with an overall response rate of 73% (CI, 45–91).[102] Median PFS and OS was 18 and 58 months, respectively. The trial was stopped early because a competitive trial was scheduled to commence.[102] In a phase II trial (GOG-86P), the combination of carboplatin and paclitaxel with bevacizumab followed by maintenance bevacizumab until progression was compared with historic controls, showing a significant OS improvement (HR 0.71; 92.2% CI, 0.33–0.91), with no differences in PFS (HR 0.81; 92.2% CI, 0.63–1.02).[103] A randomized phase II trial evaluated carboplatin and paclitaxel for six cycles with and without trastuzumab as a continuation-maintenance treatment in high-grade serous endometrial cancer with Her2/neu overexpression.[104] The study demonstrated a significant improvement in PFS with the addition of trastuzumab (8 vs. 12.6 months; HR 0.44; 90% CI, 0.26–0.76; p = .005). Other trials with Her2-targeted agents are ongoing in this population (NCT02491099). Her2 assessment should routinely be incorporated in the treatment of high-grade serous endometrial cancers.

Endometrial sarcoma As opposed to carcinomas, sarcoma of the endometrium is rare and comprises less than 3% of all endometrial malignancies, with an incidence of approximately one diagnosis per 100,000 women per year.[105] Sarcomas are aggressive tumors with a high propensity to metastasize, occur in younger individuals, and are composed of several distinct histologic entities.[105] Leiomyosarcoma (LMS) is the most common (two-thirds of cases), followed by endometrial stromal tumors, unclassified uterine sarcoma, and adenosarcoma.[105]

Surgical resection without lymph node dissection and without radiotherapy is standard for patients with primary endometrial LMS.[105] Because of high recurrence, a high metastasis rate, and chemotherapy sensitivity, adjuvant chemotherapy with doxorubicin and ifosfamide is considered for high-risk patients. The largest series to support adjuvant chemotherapy is a meta-analysis of approximately 2,000 patients with high-grade soft-tissue sarcomas who underwent surgical resection and were randomly assigned to chemotherapy versus observation.[106] Patients who received chemotherapy with doxorubicin and ifosfamide had the greatest benefit in recurrence-free survival and OS. Although this analysis included patients with LMS, it also included patients with other types of sarcoma.[106] Many sarcoma centers prefer preoperative chemotherapy to identify patients with chemotherapy-sensitive tumors, initiate treatment of microscopic metastases earlier, and do not operate on patients who are destined to develop metastatic disease shortly after surgery.

There are currently no randomized data to support the use of prolonged maintenance therapy in endometrial sarcomas after resection or after response to chemotherapy. Active chemotherapy agents include doxorubicin, ifosfamide, dacarbazine, and gemcitabine but are generally not given for prolonged periods of time without measurable disease because of the risk of serious toxicities such as leukemia, cardiomyopathy, and pneumonitis.[107-109] However, endometrial stromal tumors and low-grade LMS are more likely to express the estrogen receptor, so there is a compelling rationale to consider maintenance antiestrogen therapy for these patients.[105] Newer agents such as the multitargeted kinase pazopanib and the drug trabectedin do not appear to have serious toxicities when used for many years and thus could also be considered for maintenance therapy for patients with exceptionally high risk.[110,111] With so many active systemic therapies, there is a compelling rationale for a prospective trial of maintenance therapy in endometrial LMS and potentially other sarcomas.

CONCLUSION

Maintenance strategies in ovarian cancer are incorporated in clinical practice. Bevacizumab should be considered as the frontline treatment for patients with high-risk cancer.[11,12] PARP inhibitors have demonstrated a substantial increase in PFS and PFS2 and should be considered as first-line maintenance treatment for *BRCA*m carriers[8] as well as in platinum-sensitive relapse regardless of *BRCA*m.[5,6,9] However, caution is required because no OS benefit has been demonstrated yet with PARP inhibitors, and QOL analyses across the different maintenance strategies have not demonstrated benefit.[5,6,8,9,61] The addition of bevacizumab in cervical cancer does not incorporate a maintenance strategy as per the trial design, but it is the only targeted treatment demonstrating OS benefit in the overall population thus far and cost-effectiveness is near current willingness-to-pay standards.[93,112] The optimal number of cycles and chemotherapy schedules in recurrent platinum-resistant ovarian cancer, cervical cancer, and endometrial cancer remains controversial. In platinum-resistant, recurrent EOC, chemotherapy with or without breaks for toxicity recovery should be tailored to each patient. Future clinical trials examining the best treatment schedule are warranted. The aim to find the best treatment strategy has led to an increased reliance on biomarkers, such as the presence of HRD and loss of heterozygosity scores and bevacizumab response predictive panels; however, with the exception of *BRCA*m, none of these have been incorporated as a determining treatment factor.[5,6,39,113,114]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_238755.

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