Treatment of epithelial ovarian cancer
Lindsay Kuroki,1 Saketh R Guntupalli2

ABSTRACT

Ovarian cancer is the third most common gynecologic malignancy worldwide but accounts for the highest mortality rate among these cancers. A stepwise approach to assessment, diagnosis, and treatment is vital to appropriate management of this disease process. An integrated approach with gynecologic oncologists as well as medical oncologists, pathologists, and radiologists is of paramount importance to improving outcomes. Surgical cytoreduction to R0 is the mainstay of treatment, followed by adjuvant chemotherapy. Genetic testing for gene mutations that affect treatment is the standard of care for all women with epithelial ovarian cancer. Nearly all women will have a recurrence, and the treatment of recurrent ovarian cancer continues to be nuanced and requires extensive review of up to date modalities that balance efficacy with the patient’s quality of life. Maintenance therapy with poly ADP-ribose polymerase inhibitors, bevacizumab, and/or drugs targeting homologous recombination deficiency is becoming more widely used in the treatment of ovarian cancer, and the advancement of immunotherapy is further revolutionizing treatment targets.

Introduction

Ovarian cancer is the most lethal of the gynecologic malignancies. Despite other cancers such as endometrial cancer having higher rates of incidence, ovarian cancer mortality rates continue to be high.1 Ongoing work is important to screen and diagnose epithelial ovarian cancer (EOC) earlier, but many trials have failed to find an appropriate modality or biomarker to predict which women in the general population will develop this disease. As a result, most cases (>80%) of EOC are diagnosed at an advanced stage when tumor has spread to the peritoneal cavity and upper abdominal organs.2 This substantially reduces the ability to cure this malignancy, given that five year survival rates plummet after the disease has escaped the pelvic cavity.

Despite these statistics, treatment options tested in the past five years have revolutionized the management of EOC and more targeted therapies are on the horizon (fig 1). The treatment landscape for ovarian cancer has also begun to experience innovation in biomarker development similar to those for lung and colon cancer. This includes identification of the breast cancer BRCA gene and tumors that exhibit homologous recombination deficiency (HRD). New treatments in the sphere of poly ADP-ribose polymerase (PARP) inhibitors,3-6 immunotherapy, and heated intraperitoneal chemotherapy (HIPEC)7 have the ability to transform the treatment paradigm for ovarian cancer, substantially increasing survival for what was uniformly thought to be a fatal cancer.

This review is targeted toward gynecologic/surgical oncologists and medical oncologists who are involved in the multidisciplinary approach to ovarian cancer. We will review the epidemiology and risk factors for the development of this disease, as well as the surgical techniques vital to its treatment. Adjuvant therapies in the form of chemotherapy will be reviewed in the primary and recurrent/refractory settings. The latest controversies and avenues for future treatments and therapies are discussed.

Sources and selection criteria

We selected references for this review to reflect landmark articles that have shaped diagnosis and management of ovarian cancer over the past 20 years. We searched PubMed and Embase between 2000 and 2020 and selected peer reviewed articles in the English language by using the following search terms: ovarian cancer, neoadjuvant chemotherapy, primary cytoreductive surgery, lymphadenectomy, secondary cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, intraperitoneal chemotherapy, adjuvant chemotherapy, maintenance therapy, recurrence, platinum sensitive recurrence, platinum resistant recurrence, immunotherapy, PARP inhibitors, bevacizumab, and chimeric antigen receptor therapy (CAR-T). We also identified references from relevant review articles, as well as from the similar items section of PubMed and the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology Clinical Practice guidelines.8 9 We screened and reviewed more than 200 articles in the preparation of this manuscript. We prioritized publications within the past decade but also included more historic articles.
that were considered landmark trials that changed the treatment paradigm of ovarian cancer. We prioritized randomized controlled trials, systematic reviews, meta-analyses, observational studies, Society of Gynecologic Oncology (SGO) consensus statements, and systematic reviews published within the past 10 years. We excluded articles published in non-peer reviewed journals, case reports, and case series.

**Epidemiology and risk factors**

Epithelial ovarian cancer represents the most lethal of the gynecologic malignancies. In 2020 more than 300,000 new cases of EOC are expected worldwide, with more than 190,000 deaths.\(^{1,10}\) The median age at diagnosis is 63 years, and more than 70% of cases of EOC are diagnosed at advanced stages with five year survival rates approximating 48%.\(^{2}\)

The lifetime risk of developing EOC is 1.3%, but it is as high as 40-45% for women with a \(BRCA1\) mutation and 15-20% for \(BRCA2\) carriers.\(^{11}\) Risk factors for EOC include increasing age, infertility, endometriosis, polycystic ovarian syndrome, use of an intrauterine device, and cigarette smoking (for mucinous carcinomas). An estimated 18% of cases of EOC are associated with a germline mutation\(^{12};\) most of these are attributable to \(BRCA1\) and \(BRCA2\), but they also include other genes in the homologous recombination pathway (for example, \(TP53\), \(ATM\), \(MRE11\), \(RAD51\), \(H2AX\), \(PALB2\), \(RPA\), \(BP1\), \(BARD1\), and \(RAD52\))\(^{12-14}\) and mismatch repair genes.\(^{15-17}\)

The Cancer Genome Atlas Research Network evaluated 316 stage II through IV high grade serous ovarian cancer (HGSOC) specimens and reported that 3% of the cases showed somatic \(BRCA1/2\) mutations.\(^{18}\) Therefore, genetic screening is recommended in all patients newly diagnosed as having EOC.

**Histological subtypes**

The World Health Organization classification of tubo-ovarian tumors includes common epithelial tumors, sex cord stromal tumors, germ cell tumors, soft tissue tumors, unclassified type, and metastatic secondary tumors (5-6% of adnexal masses are metastases from breast, gastrointestinal tract, or urinary tract). Given that HGSOC is the most common histological subtype, accounting for 75% of all EOCs, we will focus on this specific subgroup. Table 1 describes the other histology subtypes, including endometrioid, clear cell, low grade serous, and mucinous, in more detail.
Surgery for ovarian cancer
Neoadjuvant chemotherapy versus primary debulking

Primary cytoreductive surgery (PCS) followed by platinum based chemotherapy remains the standard treatment for patients with advanced stage EOC. Thus, all women with suspected stage III or IV EOC should be evaluated by a gynecologic oncologist before treatment is started, to determine whether they are candidates for PCS. Neoadjuvant chemotherapy may be considered for patients with bulky stage III or IV disease whose tumors are deemed unlikely to be completely cytoreduced to no gross residual disease (R0) or for patients who are poor surgical candidates. Although the choice between PCS and neoadjuvant chemotherapy remains controversial, the SGO and American Society of Clinical Oncology (ASCO) clinical practice guidelines state that for those women who have a high likelihood of achieving a cytoreduction to less than 1 cm (ideally to no visible disease) with acceptable morbidity, PCS is recommended over neoadjuvant chemotherapy (evidence quality: intermediate; strength of recommendation: moderate). Theoretical advances in surgical cytoreduction pertain to removal of large and/or poorly vascularized tumors, thus eliminating pharmacologic sanctuaries and allowing for optimal killing of the cells of the better perfused small residual tumors that have higher growth fractions; host immunocompetence is enhanced by removal of large tumor bulk and prevention of resistance to chemotherapy. A primary clinical evaluation should include a computed tomography scan of the chest, abdomen, and pelvis to evaluate the extent of disease and the feasibility of surgical resection. In exceptional cases when a biopsy is not feasible, cytological evaluation combined with a serum cancer antigen 125 (CA-125) to carciinoembryonic antigen ratio above 25 is acceptable to confirm the primary diagnosis and exclude a non-gynecologic cancer. Should neoadjuvant chemotherapy be deemed the optimal management strategy, historical confirmation of EOC by biopsy is preferred over fine needle aspiration or paracentesis, before administration of neoadjuvant chemotherapy.

As our population is aging, a careful assessment of operability based on the patient’s age, functional and instrumental activities of daily living, performance status, comorbidities, and nutritional status is critical for preoperative planning, as these factors have been shown to predict postoperative complications, extended hospital stay, and six month mortality in older patients undergoing cancer surgery. The American College of Surgeons and the American Geriatrics Society have provided general guidelines for the preoperative assessment of older patients undergoing surgery. Patients 75 years of age or older who have at least one comorbidity have a 30 day postoperative mortality of greater than 10% after planned PCS for stage III EOC. A laparoscopic surgical assessment using the Fagotti scoring system has been studied and externally validated to determine the feasibility of PCS to no gross residual disease. Seven parameters are included in this scoring system—peritoneal carcinomatosis, diaphragmatic disease, mesenteric disease, omental disease, bowel infiltration, stomach infiltration, and liver metastasis. Mesenteric retraction was the most difficult to assess (75.2%) by laparoscopy, although stomach infiltration had the poorest negative predictive value (71.6%) and accuracy (77.3%). A review on predictors of optimal cytoreduction in patients with newly diagnosed advanced stage EOC commented that standard use of the Fagotti score should be implemented across different centers, with a predictive index value of 8 or greater shown to have the best prediction of suboptimal cytoreduction.

Four phase III trials have evaluated whether neoadjuvant chemotherapy followed by interval cytoreductive surgery (ICS) is effective and safe compared with PCS followed by platinum based chemotherapy (table 2). Results from these trials have formed the basis of clinical practice guidelines on neoadjuvant chemotherapy for newly diagnosed advanced EOC set forth by the SGO and ASCO. In each of these trials, neoadjuvant chemotherapy consisted of three to four cycles of carboplatin and paclitaxel.

Two phase III trials showed non-inferiority of neoadjuvant chemotherapy with ICS compared with PCS followed by chemotherapy. The first was the European Organization for Research and Treatment of Cancer (EORTC)-55971, a phase III

Table 1 | Histological subtypes of epithelial ovarian cancers and their common characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>High grade serous carcinoma</th>
<th>Clear cell carcinoma</th>
<th>Endometrioid carcinoma</th>
<th>Mucinous carcinoma</th>
<th>Low grade serous carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of cases</td>
<td>70</td>
<td>12</td>
<td>11</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Median age at diagnosis</td>
<td>61</td>
<td>55</td>
<td>56</td>
<td>53</td>
<td>43</td>
</tr>
<tr>
<td>Tumor marker(s)</td>
<td>CA-125</td>
<td>CA-125</td>
<td>CA-125</td>
<td>CEA, CA19-9</td>
<td>CA-125</td>
</tr>
<tr>
<td>Genetic risk factors</td>
<td>BRCA1/2</td>
<td>HNPPC</td>
<td>HNPPC/BKCA</td>
<td>Not known</td>
<td>Serous borderline tumor</td>
</tr>
<tr>
<td>Common stage at presentation</td>
<td>Advanced</td>
<td>Early</td>
<td>Early</td>
<td>Early</td>
<td>Advanced</td>
</tr>
<tr>
<td>Response to platinum based chemotherapy</td>
<td>Chemo-sensitive</td>
<td>Chemo-resistant</td>
<td>Chemo-sensitive</td>
<td>Chemo-resistant</td>
<td>Chemo-resistant</td>
</tr>
<tr>
<td>Common gene mutations</td>
<td>P53, BRCA1/2, HR defects</td>
<td>PIK3CA, ARID1A</td>
<td>PIK3CA, PTEN, MSI</td>
<td>PIK3CA, ARID1A</td>
<td>PIK3CA</td>
</tr>
<tr>
<td>Common immune profile</td>
<td>P53+, WT1+, PAX8+, Ki67</td>
<td>HNF β+, WT1-, ER</td>
<td>ER+, PAX8+, vimentin+</td>
<td>CK20+, CDx2+,</td>
<td>WT1+, PAX8+,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WT1-, P53 wild-type</td>
<td>CK7+, ER, WT1-</td>
<td>P53 wild-type, low Ki67</td>
</tr>
</tbody>
</table>

BRCA1/2=breast cancer susceptibility gene 1/2; CA-125=carcinoantigen 125; CEA=carcinoembryonic antigen; ER=estrogen receptor; HNPPC=hereditary non-polyposis colorectal cancer; HR=homologous recombination; MSI=microsatellite instability; PTEN=phosphatase and tensin homolog; STIC=serous tubal intraepithelial carcinoma; TP53=tumor protein p53;
international trial of 670 women with stage IIIC/IV EOC randomized to neoadjuvant chemotherapy with ICS versus up-front PCS. Median overall survival was equivalent (29 vs 30 months for neoadjuvant chemotherapy vs PCS), but patients who received neoadjuvant chemotherapy had fewer surgical complications. In the CHORUS trial, 550 patients with clinical stage III-IV disease were randomized to PCS followed by six cycles of chemotherapy or neoadjuvant chemotherapy. In intention to treat analysis, median overall survival for the PCS group was 22.8 months compared with 24.5 months for those undergoing neoadjuvant chemotherapy. Later, a pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials showed improved survival for patients with stage IV disease who received neoadjuvant chemotherapy followed by ICS: median overall survival 24.3 months in the neoadjuvant chemotherapy group versus 21.2 months in the PCS group (hazard ratio 0.76, 95% confidence interval 0.58 to 1.00; P=0.48) and median progression-free survival (PFS) 10.6 versus 9.7 months (0.77, 0.59 to 1.00; P=0.069).

Major criticisms of the EORTC trial relate to selection bias for patients at high risk that were not inclusive of all stage III patients and generalizability of surgical attempt to achieve R0 resection. The largest residual tumor was reported to be 1 cm or smaller in 41.6% of patients after PCS and in 80.6% of patients after ICS. As expected, median overall survival rates varied by largest residual tumor and treatment arm (neoadjuvant chemotherapy versus PCS)—overall survival was 38 versus 45 months for R0, 27 versus 32 months for R1 disease, and 25 versus 20 months for R2 disease. Despite these limitations, an exploratory analysis of the EORTC data helped to better identify which subgroups of patients with stage III-IV EOC benefit most from neoadjuvant chemotherapy versus PCS. Those with stage IIIC tumors smaller than 4.5 cm benefited more from PCS, whereas stage IV patients with metastatic tumors smaller than 4.5 cm benefited more from neoadjuvant chemotherapy.

### Importance of optimal (R0) cytoreduction
Irrespective of when surgery is performed—up front or after neoadjuvant chemotherapy in the primary setting—the goal remains removal of all visible tumor. As with PCS, maximal effort should be made to remove all gross disease in the abdomen, pelvis, and retroperitoneum. The volume of residual disease remaining after cytoreductive surgery is one of the most powerful determinants of survival for patients with EOC. One meta-analysis involving 6885 patients with stage III or IV ovarian carcinoma reported that with each 10% increase in maximal cytoreduction, a 5.5% increase in median survival time was seen.

Neoadjuvant chemotherapy should be considered when optimal cytoreduction is unlikely or would be at the cost of high perioperative morbidity and mortality. In these cases, ICS should be performed after four cycles or fewer of neoadjuvant chemotherapy for women who have achieved a response to chemotherapy or have stable disease. Another meta-analysis of 835 patients with advanced stage EOC confirmed previous findings that increasing percentage maximal cytoreduction is positively associated with median cohort survival; however, it also showed that a 4.1 month decrease in survival is seen for each extra cycle of neoadjuvant chemotherapy, suggesting that definitive operative intervention should be undertaken as early in the treatment course as possible. Ultimately, timing of surgery has not been prospectively evaluated and should be determined on an individual basis.

Bevacizumab containing regimens for neoadjuvant chemotherapy should be used with caution before ICS, given the potential for compromised postoperative healing. If bevacizumab is used as part of a neoadjuvant chemotherapy regimen, it should be withheld from therapy for at least 28 days before ICS.

### General principles of surgical cytoreduction
Surgical cytoreduction should be done by an experienced, high volume gynecologic oncologist (≥10 cases/year) at a high volume hospital (≥20 cases/
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A vertical midline abdominal incision should be used in most patients with suspected malignant EOC in whom a surgical staging procedure, a PCS, or an ICS is planned. Interest is growing in conducting a multicenter surgical trial to investigate the feasibility and safety of using a minimally invasive ICS for women who have had a complete response after three to four cycles of neoadjuvant chemotherapy with a CA-125 that has normalized. Given that nearly 75% of patients newly diagnosed as having EOC present with advanced disease, surgical procedures that may be considered for optimal cytoreduction include bowel resection and/or appendectomy, diaphragm or peritoneal stripping, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or pancreatectomy.

Cytoreductive surgery for patients at stage IV can be attempted, with 30% achieving optimal cytoreduction. A retrospective cohort study showed that survival depends on the location of the stage IV disease. Those with pleural effusion present had a median survival of 19 months compared with 12 months if lung metastasis was present, 18 months for parenchymal liver metastasis, and 26 months for those with other extraperitoneal sites.

Removal of lymph nodes for advanced stage disease has also been studied. Some retrospective studies have suggested a potential survival benefit from systematic pelvic and para-aortic lymphadenectomy in patients with macroscopically resected advanced EOC, although these studies are inherently flawed by selection bias.

A landmark randomized international trial studied 427 patients with stage IIB, IIIC, or IV disease, all of whom had optimal surgery and were randomized intraoperatively to systematic pelvic and para-aortic lymphadenectomy versus resection of bulky nodes only. All patients received adjuvant platinum-based chemotherapy. The five year progression-free interval was 31.2% for the lymphadenectomy group compared with 21.6% for the control arm, with no difference in the risk of death. Patients in the lymphadenectomy group were more likely to need blood transfusions and had longer surgery and more postoperative complications. Although highly cited, this study was criticized for several reasons: participating surgeons were not required to prove proficiency in performing a complete lymphadenectomy, thus contributing to heterogeneity of surgical quality among participating centers; resection of bulky nodes was permitted in the no lymphadenectomy arm; and more than two thirds of included patients had residual postoperative intra-abdominal disease, which makes interpreting the potential benefit of lymphadenectomy difficult. Ultimately, because of these limitations, results of this trial did not change practice.

Learning from these previous criticisms, the Lymphadenectomy in Ovarian Neoplasms (LION) trial emerged. This was a randomized controlled trial of 647 patients intraoperatively randomized to either undergo systematic pelvic and para-aortic lymphadenectomy or not undergo lymphadenectomy if macroscopic complete resection was achieved and the patient had normal lymph nodes both before and during surgery. Median overall survival, the primary outcome, was 69.2 months in the no lymphadenectomy group and 65.5 months in the lymphadenectomy group (hazard ratio 1.06, 0.83 to 1.34; P=0.65). Median PFS was 25.5 months in both groups, and postoperative morbidity was higher in the lymphadenectomy group, including percentage of patients receiving transfusions (63.7% v 56%; P=0.005), incidence of infections treated with antibiotics (25.8% v 18.6%; P=0.03), repeat laparotomy (12.4% v 6.5%; P=0.01), and mortality within 60 days after surgery (3.1% v 0.9%; P=0.049). Taken together, these data suggest that patients with advanced EOC with normal lymph nodes both before and during surgery who undergo macroscopically complete resection do not benefit from systematic pelvic and para-aortic lymphadenectomy.

**Hyperthermic intraperitoneal chemotherapy after cytoreduction**

HIPEC with cisplatin (100 mg/m²) can be considered at the time of interval cytoreductive surgery for stage III disease (see section below). A phase III multicenter trial recently published results showing that the addition of HIPEC as a single administration of intraperitoneal chemotherapy to ICS improved recurrence-free survival (RFS) by 3.5 months and overall survival by 11.8 months compared with surgery alone, without increasing perioperative morbidity. The trial included 245 patients with stage III EOC who had at least stable disease after three cycles of neoadjuvant carboplatin and paclitaxel, who were randomized at the time of ICS when incomplete or optimal site of reduction was anticipated. Median RFS, the primary endpoint, was 10.7 months in the surgery group and 14.2 months in the surgery plus HIPEC group. The median overall survival was 33.9 months in the surgery group and 45.7 months in the surgery plus HIPEC group. The percentage of patients who had adverse events of grade 3 or 4 was similar in the two groups (25% in the surgery group and 27% in the surgery plus HIPEC group; P=0.76). Furthermore, although the overall percentage of bowel resections performed was similar in the two groups (34% for both), the HIPEC arm had a higher rate of colostomy/ileostomy than the surgery arm (21/29 (72%) v 13/30 (43%); P=0.04). This higher rate was attributed to surgeons’ preference, given that no evidence suggests that HIPEC for ovarian cancer is associated with higher rates of anastomotic leakage. This study certainly fills a gap in the literature and provides another option for management, but HIPEC has not been widely adopted and should be practiced at institutions that have expertise in both delivery of HIPEC and management of complications that may ensue.
Primary adjuvant therapy

Adjuvant therapy for early stage ovarian cancer patients

The decision to recommend adjuvant therapy for patients with early stage EOC should be individualized according to histology, risk factors, adequacy of staging, comorbidities, and likelihood of response to platinum based chemotherapy. Observation is recommended for those with optimally staged IA or IB, grade 1 endometrioid carcinomas and other histology given that five year survival rates are greater than 90% with surgical treatment alone.47 48 If adjuvant therapy is recommended, three to six cycles are generally recommended.49 50 A retrospective analysis of GOG157, which compared three versus six cycles of adjuvant carboplatin and paclitaxel, showed improved RFS with six cycles among patients with HGSO. Among non-serous tumors, no difference was observed between three and six cycles. The European Organization for Research and Treatment of Cancer-Adjuvant Chemotherapy in Ovarian Neoplasm (EORTC-ACTION) and the International Collaborative Ovarian Neoplasm (ICON1) trial were set up as parallel, complementary studies.44-50

In the ICON1 trial, chemotherapy (cisplatin, doxorubicin, and paclitaxel) was compared with surgery alone. The trial was stopped prematurely due to a lack of difference in survival between the two groups.44 In the EORTC-ACTION trial, patients received six cycles of cisplatin and paclitaxel vs surgery alone.45 In both studies, the chemotherapy arm showed higher grade 3-4 neutropenia (94% v 84%; difference: 11%, 95% confidence interval 7% to 14%; P<0.001) but improved grade 2 or higher neurotoxicity (11% v 30%; 15% to 24%; P<0.001).41

Intravenous versus intraperitoneal chemotherapy

In women with optimally cytoreduced, ideally no gross residual, disease who have not received neo-adjuvant chemotherapy, intravenous chemotherapy, or a combination of intravenous and intraperitoneal chemotherapy is a reasonable option. The appeal of intravenous/intraperitoneal chemotherapy stems from the need to optimize penetration of diffusion limited drugs, such as cisplatin, in a disease that is largely locoregional and characterized by peritoneal carcinomatosis. Four landmark trials (table 3) have been published since 1996,62-65 three showing survival benefit of intraperitoneal over intravenous chemotherapy, even among both R1 and R0 groups, and with larger magnitude of benefit in women who completed all six cycles and who had a BRCA mutation.66 However, despite the strong rationale and survival efficacy, intraperitoneal chemotherapy for EOC is inconsistently used as standard frontline treatment.67 Several barriers affect the acceptance of intraperitoneal chemotherapy, including catheter related complications and higher rates of toxicities such as gastrointestinal adverse events, neutropenia, thrombocytopenia, and neurotoxicity. Quality of life was worse for patients treated with intraperitoneal chemotherapy, although it was comparable one year after completion except for neuropathy.68

The most recent trial, GOG252,65 was intended not only to reduce the toxicities of the GOG172 regimen64 but also to incorporate a biologic targeted therapy, bevacizumab, as a primary therapy and maintenance, similar to GOG218. It failed to show a PFS benefit of intraperitoneal chemotherapy (26.8 v 28.7 months) or intraperitoneal cisplatin (26.8 v 27.8 months) compared with intravenous chemotherapy. One of the major criticisms of this trial was the fact that bevacizumab was used across all study arms, perhaps limiting the effect size of intraperitoneal therapy but, nevertheless, allowing the control arm to outperform (PFS 23.8 months) historical controls from GOG172 (18.3 months).

Dose dense chemotherapy

Dose dense intravenous therapy has also been compared with conventionally dosed intravenous therapy (every three weeks) as a first line treatment strategy in EOC with mixed results. Notable trials...
include the Japanese GOG3016 trial, which compared carboplatin and paclitaxel every three weeks with carboplatin (every three weeks) and weekly paclitaxel, showing a significant benefit in PFS (28 v 17.5 months; hazard ratio 0.76, 0.62 to 0.91) and overall survival (median 100.5 v 62 months; 0.79, 0.63 to 0.99) compared with conventional treatment.\(^{69}\) Although anticipated, the same survival benefit was not shown in the US. In GOG262, women with stage II-IV EOC were randomized either to conventionally dosed carboplatin and paclitaxel or to dose dense therapy (carboplatin every three weeks plus weekly paclitaxel). Bevacizumab was allowed in both arms and administered to 84% of the study population.\(^{70}\) The primary endpoint, PFS, was not significantly improved among women who received weekly paclitaxel compared with a regimen of treatment every three weeks. However, in the subgroup of patients who did not receive bevacizumab, weekly paclitaxel led to a PFS that was 3.9 months longer than that observed with paclitaxel administered every three weeks (14.2 v 10.3 months; hazard ratio 0.62, 0.40 to 0.95; \(P=0.03\)).

ICON8 involved similar study arms, comparing carboplatin and paclitaxel every three weeks (control, arm 1) versus either carboplatin (AUC 5 or 6) every three weeks and dose dense paclitaxel (80 mg/m\(^2\) weekly) (arm 2) or weekly carboplatin (AUC 2) plus paclitaxel (80 mg/m\(^2\)) (arm 3).\(^{71}\) In this phase III trial involving 1566 women with IC-IV EOC, no significant PFS increase was observed with either weekly regimen (24.4 months control versus 24.9 arm 2 versus 25.3 arm 3). Grade 3-4 toxicities were higher with the dose dense arms (42% v 62% v 53%).

### Chemotherapy considerations for older patients

Although carboplatin as a single agent has been advocated as a less toxic option, particularly in frail or elderly patients, a randomized trial of patients aged 70 years or older with stage III/IV EOC and determined by geriatric assessment to be vulnerable showed worse survival outcomes with single agent carboplatin compared with carboplatin and paclitaxel every three weeks or weekly.\(^{72}\) This led to premature closure of the trial. GOG273 studied the same age group of women (\(\geq 70\) years) with newly diagnosed stage III/IV EOC who underwent adjuvant chemotherapy according to the physician’s choice of either single agent carboplatin (AUC 5), carboplatin (AUC 5) plus paclitaxel (135 mg/m\(^2\)) every three weeks, or carboplatin (AUC 5) plus weekly paclitaxel (60 mg/m\(^3\)). Although the trial is still ongoing, the authors reported their primary results, which showed that the instrumental activities of daily living score could predict the completion of four cycles of chemotherapy.\(^{73}\)

A modified dose dense regimen (carboplatin (AUC 2) plus paclitaxel (60 mg/m\(^2\)) every week for 18 weeks) studied in the MITO7 phase III trial, was shown to offer better tolerability than conventional dosing and is often considered for medically frail patients.\(^{74}\) It was associated with decreased grade 3-4 neutropenia (42% v 50%), febrile neutropenia (0.5% v 3%), grade 3-4 thrombocytopenia (1% v 7%), and grade 2 or worse neuropathy (6% v 17%).

### Maintenance after primary adjuvant therapy

**Paclitaxel**

The role for maintenance therapy is supported by GOG178, a phase III trial comparing three versus 12 months of paclitaxel 175 mg/m\(^2\) every four weeks for 12 cycles after completion of six cycles of platinum/paclitaxel with a clinical complete response among patients with stage III/IV EOC.\(^{75}\) This study closed early after 50% enrollment and an interim analysis that showed an improved PFS favoring 12 cycles (28 v 21 months; hazard ratio 2.31, 1.08 to 4.94; \(P=0.002\)). However, a follow-up study showed a PFS of 22 versus 14 months with no overall survival benefit.\(^{76}\) As expected, the only major difference with

### Table 3 | GOG trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Study groups</th>
<th>Progression-free survival</th>
<th>Overall survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Length (months)</td>
<td>Effect size (95% CI)</td>
</tr>
<tr>
<td>GOG 104(^{77})</td>
<td>Cisplatin 100 mg/m(^2) IV; cyclophosphamide 600 mg/m(^2) IV; Q3 wks (\times) 6 cycles</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>GOG 114(^{43})</td>
<td>Cisplatin 100 mg/m(^2) IP; cyclophosphamide IV; Q3 wks (\times) 6 cycles</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>GOG 172(^{78})</td>
<td>Carboplatin (AUC 9) IV every 4 wks (\times) 2; D1 taxol 135 mg/m(^2) (24 h) IV; D2 cisplatin 100 mg/m(^2) IP Q3 wks (\times) 6</td>
<td>22.2</td>
<td>RR 0.78 (0.66 to 0.94)</td>
</tr>
<tr>
<td>GOG 252(^{79})</td>
<td>D1 taxol 135 mg/m(^2) (24 h); D2 cisplatin 100 mg/m(^2) IV</td>
<td>23.8</td>
<td>RR 0.80 (0.64 to 1.00)</td>
</tr>
</tbody>
</table>

bev=bevacizumab; D=day; HR=hazard ratio; IP=intraperitoneal; IV=intravenous; NR=not reported; RR=relative risk; taxol=paclitaxel; wks=weeks.
regard to toxicity was higher incidence of treatment related grade 2/3 peripheral neuropathy in the 12 cycle treatment arm (15% v 23%), although no information was available on how long symptoms persisted after discontinuation of treatment. Criticisms of this trial include the allowance of information was available on how long symptoms 23%), although no cycle treatment arm (15% v 23%) related grade 2/3 peripheral neuropathy in the 12 cycles, patients were randomized to either observation or weekly paclitaxel for 24 weeks. No differences were seen in either probability of five year recurrence or survival.

Pazopanib, an oral, multitarget kinase inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, platelet derived growth factor receptors α and β, and proto-oncogene receptor tyrosine kinase, has also been studied in this setting. The AGO-OVAR16 trial included 940 patients with stage II-IV EOC and no evidence of progression after five or more cycles of platinum-taxane chemotherapy, randomized to pazopanib or placebo for up to 24 months.58 PFS, the primary endpoint, was prolonged in the pazopanib arm (7.9 v 12.3 months; hazard ratio 0.77, 0.64 to 0.91; P=0.0021). This effect held true regardless of BRCA status, although a more dramatic benefit was seen among BRCA1/2 carriers. Common adverse events associated with pazopanib included hypertension, diarrhea, nausea, headache, fatigue, and neutropenia.

Angiogenesis inhibition
Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). Given its non-overlapping toxicity profile with systemic chemotherapy, it is generally well tolerated, but it does come with serious adverse effects such as hypertension, proteinuria, hemorrhage, thrombosis, and life threatening bowel perforation. It has been studied in combination with chemotherapy followed by single agent bevacizumab maintenance therapy in two landmark trials, ICON7 and GOG0218, in the upfront setting among patients with advanced EOC.75,76 Both trials showed a modest improvement in PFS with incorporation of concurrent and maintenance bevacizumab compared with surveillance only. This led to European Medicines Agency (EMA) approval of frontline bevacizumab in the European Union in 2011, and ultimately approval by the US Food and Drug Administration (FDA) along with maintenance bevacizumab for advanced EOC on June 13, 2018. However, neither ICON7 nor GOG218 showed a difference in overall survival. A predefined subgroup analysis of 502 patients with a poor prognosis in ICON7 showed an overall survival benefit among patients who received bevacizumab plus chemotherapy compared with those who received chemotherapy alone (restricted mean survival time 34.5 (95% confidence interval 32.0 to 37.0) months with standard chemotherapy versus 39.3 (37.0 to 41.7) months with bevacizumab; log-rank P=0.03).78 High risk of progression was defined as stage IV disease, inoperable stage III disease, or suboptimally debulked (>1 cm) stage III disease. Although GOG218 also enrolled patients with high risk disease, crossover to bevacizumab after progression may have contributed to the discordance between PFS benefit without significant improvement in overall survival. GOG218 was unable to validate the overall survival benefit seen in ICON7, even after classifying patients according to ICON7 high risk criteria, but it did show an improved PFS and overall survival specifically in women with ascites,80 stage IV disease, or BRCA1/2 mutations or those non-BRCA1/2 carriers who were homologous recombination deficient.79 Although studies have validated the clinical role of VEGF inhibition, given the modest benefit in PFS to approximately additional four months in exchange for six cycles of concurrent therapy followed by single agent maintenance extending beyond a year, without objective clinical benefit on quality of life or overall survival, this targeted management strategy should be individualized. Reserving bevacizumab for management of recurrent disease is reasonable (discussed later).

Poly ADP-ribose polymerase inhibition
Other maintenance strategies after first line chemotherapy, beyond VEGF inhibition, include PARP inhibitors. The optimal agent in this setting remains under investigation, but targeted therapies are being tested in phase III clinical trials. Two PARP inhibitors are approved by the FDA for maintenance therapy after response to first line platinum. Olaparib received FDA approval on the basis of SOLO-1, a phase III randomized, double blind, placebo controlled, multicenter trial evaluating the efficacy and safety of olaparib as maintenance monotherapy compared with placebo, in 391 patients with newly diagnosed advanced BRCA mutated ovarian cancer following platinum based chemotherapy.3 Olaparib reduced the risk of disease progression or death by 70% (hazard ratio 0.30, 0.23 to 0.41; P<0.001), and at 41 months’ follow-up the median PFS for patients treated with olaparib was not reached compared with 13.8 months for patients treated with placebo. More recently, olaparib plus bevacizumab received FDA approval as first line maintenance treatment for patients with ovarian cancer who have complete or partial response to first line platinum based chemotherapy and whose cancer is associated with HRD, defined by either deleterious or suspected BRCA mutation and/or genomic instability. This expanded indication for olaparib was based on the PAOLA-1 trial (ClinicalTrials.gov identifier NCT03737643). This was a phase III, randomized, double blind, placebo controlled, multicenter trial of 806 women with stage III-IV high grade serous or endometrioid EOC who responded to first line platinum taxane chemotherapy plus bevacizumab. It showed a PFS benefit of 4.5 months among patients randomized
to olaparib plus bevacizumab maintenance versus placebo plus bevacizumab (22.1 vs 16.6 months; hazard ratio for disease progression or death 0.59, 0.49 to 0.72; P<0.001). This survival benefit also extended to patients with tumors showing HRD regardless of BRCA status.

Veliparib (VELIA trial; NCT02470585) and niraparib (PRIMA trial; NCT02655016) maintenance therapy have also been studied, both showing improvement in PFS relative to placebo in patients with newly diagnosed advanced EOC who respond to platinum-based chemotherapy. Notable highlights of each trial are summarized here. VELIA randomized patients 1:1:1 to three treatment arms—chemotherapy plus placebo followed by placebo maintenance (control), chemotherapy plus veliparib followed by placebo maintenance (veliparib combination only arm), or chemotherapy plus veliparib followed by veliparib maintenance (veliparib throughout arm). Benefit in PFS was seen only in the veliparib throughout cohort compared with control (23.5 vs 17.3 months; hazard ratio 0.68, 0.56 to 0.83). PRIMA, on the other hand, was a randomized, double-blind, phase III trial that randomized 733 women 2:1 to receive niraparib or placebo maintenance after response to platinum-based chemotherapy. Among patients with HRD, median PFS was significantly longer in the niraparib group compared with placebo (21.9 vs 10.4 months; hazard ratio for progression or death 0.43, 0.31 to 0.59; P<0.001). This benefit also remained when the overall population was analyzed (13.8 vs 8.2 months; hazard ratio 0.62, 0.50 to 0.76; P<0.001). These trials reinforce the importance of identifying a patient’s BRCA status at the time of diagnosis. Furthermore, the FDA approved the Myriad myChoice CDx (Myriad Genetic Laboratories, Inc) as a companion diagnostic for niraparib and olaparib.

Ongoing and future studies
Continuing to build on the successes of the aforementioned trials is imperative. Ongoing studies are exploring shared pathways between PARP inhibitors, antiangiogenics, and immune checkpoint inhibitors. JAVELIN Ovarian PARP 100 (NCT03642132) was a phase III, randomized, open-label, multicenter trial investigating avelumab in combination with and/or as a maintenance label, multicenter trial investigating avelumab (NCT03642132) was a phase III, randomized, open-checkpoint inhibitors. JAVELIN Ovarian PARP 100 PARP inhibitors, antiangiogenics, and immune studies are exploiting shared pathways between aforementioned trials is imperative. Ongoing for niraparib and olaparib.

Genetic Laboratories, Inc) as a companion diagnostic the FDA approved the Myriad myChoice CDx (Myriad BRCA status at the time of diagnosis. Furthermore, patients who are in complete clinical remission after their initial treatment should receive close surveillance follow-up every three to four months for years 0-2, every four to six months for years 2-3, every six months from years 3-5, and then annually after five years. These visits should include symptom management, examination by a physician including a pelvic examination, and long-term wellness care. Patients should be educated about the signs and symptoms of recurrence, particularly pelvic pain, bloating, early satiety, obstruction, unintentional weight loss, and fatigue. The NCCN also recommends that referral for genetic risk evaluation should be done if not previously performed.

If the CA-125 concentration was initially elevated, measurement of CA-125 or other tumor markers is recommended during surveillance follow-up. The sensitivity and specificity of CA-125 for detecting recurrences range from 62% to 94% and from 91% to 100%, respectively. However, data suggest that treating recurrence early on the basis of detectable CA-125 concentrations in patients who are asymptomatic may not lead to an increase in survival and may be associated with a decreasing quality of life. Supportive of this, the EORTC conducted a randomized trial assessing the outcome of 527 patients who were treated for recurrent EOC based on CA-125 alone compared with clinically evident recurrence. Overall survival did not differ between the groups, and the authors concluded that routine measurement of CA-125 is not warranted for disease surveillance. Similarly, a post hoc analysis of patients with recurrent, platinum resistant EOC in the AURELIA trial showed that progression of disease was detected earlier by imaging than by CA-125, but this did not lead to any meaningful difference in overall survival.

Thus, imaging should be obtained when recurrence is suspected and may include computed tomography scan of the chest, abdomen, and pelvis (sensitivity 40-93%, specificity 50-98% for recurrent disease). However, given the limitations of computed tomography scans to detect small volume disease, other imaging modalities may be considered, including magnetic resonance imaging (sensitivity 62-91%, specificity 40-100%) or positron emission tomography (sensitivity 45-100%, specificity 40-100%). Ultrasoundography may be particularly useful for patients who have undergone fertility sparing surgery.
**Recurrent ovarian cancer**

**Platinum sensitivity**

Platinum sensitivity is generally defined as an interval of greater than six months between the last cycle of platinum based chemotherapy (PBC) and the start of the subsequent course of platinum. Approximately 60-70% of patients with a platinum-free interval (PFI) of more than 24 months will likely respond to re-treatment with platinum. Although the way PFI is defined varies—whether by serology only or by radiographic findings of progressive disease—studies have sought to test the hypothesis that prolonging the PFI with a non-platinum agent may improve the subsequent response to platinum.91-93 The OVA301 study is an important trial to highlight differences in practice across the world and the practical challenges we face for patients with partially platinum sensitive recurrence with a PFI of six to 12 months. Although OVA301 also included platinum resistant patients, a post hoc analysis of 214 cases with partially platinum sensitive relapse (PFI of 6-12 months)94 showed that the combination of trabectedin plus pegylated liposomal doxorubicin (PLD) versus PLD alone delayed subsequent platinum treatment by 2.5 months and led to an improved PFS (7.4 v 5.5 months; hazard ratio 0.65; P=0.015) and a 41% decrease in the risk of death (overall survival 23 v 17.1 months; hazard ratio 0.59; P=0.0015).95 On the basis of these results, trabectedin-PLD combination was approved in the European Union for patients with platinum sensitive recurrent EOC, but the US FDA required additional data to support the combination. The final overall survival analysis of 672 women (522 deaths) did not meet the protocol defined criterion for statistical significance (95% confidence interval 0.72 to 1.02; P=0.0835).96 The study was originally powered to detect a 33% increase in overall survival. Of note, an unexpected imbalance of PFI was seen, favoring the PLD arm. An ad hoc prognostic factor adjusted analysis of overall survival suggested that a benefit might have been seen in patients treated with trabectedin-PLD if the PFI were balanced between study arms. INOVATION, a prospective phase III trial comparing trabectedin-PLD followed by platinum versus PBC (NCT01379989), has completed accrual, and we are currently awaiting trial results.

Results from MITO8 are consistent with the final analysis of OVA301 and call into question whether a survival benefit is gained by extending the PFI among patients with partially platinum sensitive EOC that recurs after six to 12 months.97 This was an international, multicenter, open label phase III randomized controlled trial in 215 patients, comparing non-platinum based chemotherapy (NPBC) followed by PBC at subsequent relapse with the standard sequence of PBC followed by NPBC.97 NPBC was PLD in more than 85% of cases. PFI was prolonged in the experimental arm (7.8 v 0.01 months), but no overall survival benefit was seen, and quality of life was significantly worse in the experimental arm. The meaning of PFI only becomes more convoluted when we consider the current era of maintenance therapies after first line treatment, including PARP inhibitors and bevacizumab.

**Surgery for recurrent ovarian cancer**

Recent data on the role of secondary cytoreductive surgery from prospective randomized trials have filled a gap in the literature in an era when maintenance therapy with bevacizumab, PARP inhibitors, or both is quickly becoming a mainstream strategy with proven PFS benefit among patients with platinum sensitive, recurrent disease. GOG213 was an open label, phase III, multicenter, international, randomized clinical trial of 485 patients with platinum sensitive, recurrent EOC who had received one previous therapy and whose disease the investigator determined to be resectable.98 Women were randomized 1:1 either to secondary surgical cytoreductive surgery followed by adjuvant PBC or to receive PBC alone. Choice of adjuvant chemotherapy (paclitaxel-carboplatin or gemcitabine-carboplatin) and bevacizumab was left to the treating physician. With regard to the primary endpoint, the study showed that secondary surgical cytoreduction followed by chemotherapy did not result in longer overall survival than chemotherapy alone (median overall survival 50.6 v 64.7 months; hazard ratio for death 1.29, 0.97 to 1.72; P=0.08). This effect was not altered after adjustment for PFI and chemotherapy choice. Median PFS was 18.9 months and 16.2 months, and the hazard ratio for disease progression or death was 0.82 (0.66 to 1.01). As highlighted in the authors’ discussion, dilution of an independent surgical effect could be due to selection bias of patients who were considered to have “substantial platinum-sensitivity” with a median PFI of 20.4 months and relatively limited tumor volume, with more than half having two or fewer sites of recurrence.

Two phase III randomized clinical trials are evaluating this clinical question: an Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) trial entitled Descriptive Evaluation of Preoperative Selection Criteria for Operability in Recurrent EOC (DESKTOP) III (NCT01166737) and Surgery or Chemotherapy in Recurrent Ovarian Cancer (SOC 1; NCT01611766). The Netherlands SOcCeR trial (NTR3337) recently closed to accrual, and we anxiously await the results. Presented as an abstract at the ASCO meeting in 2017, preliminary results from DESKTOP III suggested a PFS benefit of 5.6 months (19.6 v 14.0 months; P<0.001) and longer time to the start of subsequent chemotherapy (21.0 v 13.9 months; P<0.001) among women with platinum sensitive recurrent EOC who underwent secondary cytoreduction versus a platinum containing second line therapy. The primary endpoint of overall survival is still not mature.99 The most notable differences between GOG213 and DESKTOP III lay in the patient selection criteria and adjuvant therapy, particularly the rate of maintenance bevacizumab (84% and 20%, respectively). Taken together, maturity of data from DESKTOP III and the other two trials will...
hopefully bring clarity to the value of surgery in this patient population.

**Platinum sensitive recurrence**

*Platinum based chemotherapy for recurrent disease*

Individualization of management strategies should consider previous tolerance of chemotherapy, residual symptoms, and current performance status. We recognize that not all patients are candidates for platinum doublets, but the modest PFS benefit of combination therapy compared with single agent platinum should be factored into the shared decision making. Table 4 lists landmark trials that have helped to shape the landscape of chemotherapy for patients with recurrent, platinum sensitive EOC.[100-105] ICON4/OVAR2.2 was the first phase III randomized controlled trial comparing platinum monotherapy with platinum and paclitaxel therapy in women with relapsed EOC.[100] The benefit in overall survival (29 v 24 months; hazard ratio 0.82; P=0.02) and PFS (12 v 9 months; 0.76; P<0.001) with combination therapy set the stage for future trials that often use the platinum-taxane combination as a reference group. This finding was also confirmed in a meta-analysis, which showed that combination PBC was associated with improved overall survival (hazard ratio 0.80; P=0.05) and PFS (0.68; P<0.001).[106]

Separate subgroups analysis defined by previous paclitaxel exposure, PFI (6-12 v 12 months), or number of previous lines of chemotherapy did not show a difference in the relative effect of combination chemotherapy on either PFS or overall survival.

Subsequent trials aimed to study different platinum combinations that would confer survival benefit while minimizing toxicities. A phase III randomized controlled trial showed that the combination of gemcitabine plus carboplatin versus carboplatin improved PFS by 2.8 months (8.6 v 5.8 months; hazard ratio 0.72; P=0.003), with no difference in overall survival and increased myelosuppression (70% had grade 3-4 neutropenia and 35% had grade 3-4 thrombocytopenia). Similarly, the non-inferiority randomized controlled trial CALYPSO showed that carboplatin and PLD compared with carboplatin and paclitaxel improved median PFS (11.3 v 9.4 months; hazard ratio 0.82; P=0.005) without an overall survival benefit (hazard ratio 0.99; P=0.87) at the expense of increased hand-foot syndrome (12.0% v 2.2%), nausea (35.2% v 24.2%), and mucositis (13.9% v 7%).[102-107]

**Bevacizumab**

Bevacizumab has been studied extensively in patients with platinum sensitive tumors, in combination with chemotherapy and followed by single agent maintenance therapy—OCEANS, GOG213, and AGO-OVAR2.21 (table 4). The prolongation in PFS by four months in this setting is what led to approval by the US FDA and the EMA for the treatment of platinum sensitive, recurrent EOC.

One of the more practical challenges that oncologists face is whether to re-treat with bevacizumab in a patient with platinum sensitive EOC who has already received bevacizumab as part of the first line treatment of her disease. Presented in abstract form at ASCO’s 2018 annual meeting, MITO16B-MaNGO OV2B-ENGOT OV17 (NCT01802749) considered this question and showed a prolongation of PFS by three months (11.8 v 8.8 months; hazard ratio 0.51, 0.41 to 0.64; P=0.001) in patients with platinum sensitive, recurrent EOC re-treated with bevacizumab plus concomitant second line chemotherapy (carboplatin-paclitaxel, carboplatin-gemcitabine, or carboplatin-PLD) followed by bevacizumab maintenance compared with platinum doublet chemotherapy alone.[108] Median overall survival was 27.1 months and 26.7 months without and with bevacizumab (hazard ratio 1.00, 0.73 to 1.39; P=0.98), with no unexpected toxicity.

**PARP inhibitors**

Both the FDA and EMA have approved three different PARP inhibitors to expand the armamentarium of targeted therapeutics for patients with EOC (table 5). PARP inhibitors were first approved for use as single agents in patients with recurrent EOC with deleterious germline or somatic *BRCA* mutations who had not responded to previous lines

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary outcome</th>
<th>Study groups</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Length (months)</td>
<td>Hazard ratio (95% CI)</td>
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<td>ICON4</td>
<td>OS</td>
<td>Carboplatin</td>
<td>10</td>
<td>0.76 (0.66 to 0.89)</td>
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<tr>
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<td>Carboplatin</td>
<td>5.8</td>
<td>0.72 (0.58 to 0.90)</td>
</tr>
<tr>
<td>CALYPSO</td>
<td>PFS</td>
<td>Carboplatin</td>
<td>9.4</td>
<td>0.82 (0.72 to 0.94)</td>
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<tr>
<td>OCEANS</td>
<td>PFS</td>
<td>Carboplatin</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>GOG 213</td>
<td>PFS</td>
<td>Carboplatin</td>
<td>8.4</td>
<td>0.48 (0.39 to 0.61)</td>
</tr>
<tr>
<td>AGO-OVA 2.21</td>
<td>PFS</td>
<td>Carboplatin</td>
<td>12.4</td>
<td></td>
</tr>
<tr>
<td>ENGOT</td>
<td>PFS</td>
<td>Carboplatin</td>
<td>10.4</td>
<td>0.63 (0.53 to 0.74)</td>
</tr>
</tbody>
</table>

*OS based on audited treatment-free interval stratification data; hazard ratio 0.823 (0.68 to 0.996); P=0.0447.*
of chemotherapy. However, the substantial PFS advantage that is sustained with maintenance PARP inhibition after response to PBC has made them the preferred strategy in this setting, especially among patients who harbor a germline or somatic BRCA mutation. This benefit has also extended to those who have HRD and, although to a lesser degree, to patients with BRCA wild-type and even to patients who have residual disease after responding to PBC. However, a benefit in overall survival has not yet been shown owing to the need for longer follow-up.

A practical dilemma that we will be faced with is the management strategy to treat patients who have recurrent platinum sensitive ovarian cancer and have been previously treated with frontline PARP maintenance. In this situation, enrolling the patient in a clinical trial would be the first recommendation, but inevitability oncologists will be faced with the decision between maintenance bevacizumab and rechallenge with PARP inhibitor. For the latter, whether the PARP inhibitor should be the same as the one used previously or a different brand remains unclear. An abstract presented at the 2019 SGO annual meeting described a retrospective, multi-institutional study of 22 patients with EOC that investigated previous exposure to PARP inhibitor. Treatment with a second PARP inhibitor most often involved niraparib (10; 45%), olaparib (6; 27%), or rucaparib (6; 27%), with none using veliparib, and the most common reason for discontinuing treatment was progression (13; 59%) followed by toxicity (6; 27%). Until more research is forthcoming, selection of maintenance therapy should be based on considerations of current and potential toxicities related to each therapy as well as response to previous therapies. Mechanisms of resistance to PARP inhibitors and prediction of resistance are important areas of ongoing research.

Four randomized phase III trials have reported their outcomes on PARP inhibitor maintenance for patients with platinum sensitive, recurrent EOC (table 6), all supporting the clinical benefit of using PARP inhibitors as maintenance therapy for those who are responding to PBC.610-112 NOVA and ARIEL3 extended their inclusion criteria to encompass patients regardless of their BRCA status and investigated the impact of other biomarkers, such as loss of heterozygosity/homologous recombination status, to predict response to treatment.111112 Other notable discrepancies related to the inclusion criteria are BRCA mutation status and amount of residual disease allowed. Furthermore, even though PFS was consistently chosen as the primary outcome, the method of assessment differed between studies—all but STUDY19 used investigator assessed PFS only.6

**Future directions for PARP inhibitors**

The current landscape of trials for platinum sensitive recurrent EOC is exciting and quickly expanding, with trials that are investing not only the role of PARP inhibitors in combination with antiangiogenic agents or immune checkpoint inhibition (discussed below) but also the concept of PARP inhibitor maintenance retreatment. Combining molecular targeted therapies for women with platinum sensitive recurrent EOC, particularly for those who lack a known BRCA mutation, is another important area of research. A randomized, phase II trial of 90 women with measurable, platinum sensitive recurrent EOC showed that the combination of olaparib with cediranib versus olaparib alone significantly improved median overall response rate (ORR) by 32% and median PFS by 8.7 months (17.7 vs 9.0 months; hazard ratio 0.42, 0.23 to 0.76; P=0.005).113 As expected, grade 3-4 adverse events were more common with the combination therapy, including fatigue (27% v 11%), diarrhea (23% v 0%), and hypertension (39% v 0%). Subset analysis showed significant benefit on PFS in gBRCA wild-type/unknown patients receiving olaparib-cediranib compared with olaparib alone (16.5 v 5.7 months; P=0.008). More recently, a press release from AstraZeneca and Merck reported that the addition of cediranib to olaparib did not result in improved PFS in comparison with PBC in patients with platinum sensitive recurrent EOC, which was the primary endpoint of the phase III NRG-GY0004 trial.114 Phase II AVANOVA (NCT02354131) will randomize patients with platinum sensitive recurrent EOC to either niraparib or niraparib plus bevacizumab.

Other current research initiatives are studying the role of PARP inhibitors after exposure to initial PARP inhibitors used upfront as first line maintenance therapy. The MOLTI (Multi-maintenance Olaparib After Disease Recurrence in Participants With Table 5 | Poly ADP-ribose polymerase (PARP) inhibitors for patients with epithelial ovarian cancer (EOC)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time of approval</th>
<th>Agency</th>
<th>Indications</th>
<th>BRCA status</th>
<th>Clinical setting</th>
<th>Dosing</th>
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<tr>
<td>Olaparib</td>
<td>December 2018</td>
<td>FDA</td>
<td>Advanced EOC, post CR/PR to platinum based chemotherapy</td>
<td>g/sBRCA</td>
<td>First line maintenance</td>
<td>300 mg BID</td>
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<tr>
<td></td>
<td>August 2017</td>
<td></td>
<td>Platinum sensitive recurrent OC, post CR/PR</td>
<td>gBRCA</td>
<td>Monotherapy, fourth line</td>
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<td></td>
<td>February 2018</td>
<td>EMA</td>
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<td>Rucaparib</td>
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<td>Advanced OC</td>
<td>g/sBRCA</td>
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<td>Niraparib</td>
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<td>g/sBRCA</td>
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<td>300 mg QD</td>
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<tr>
<td></td>
<td>September 2017</td>
<td>EMA</td>
<td>Platinum sensitive recurrent HGSO, post CR/PR</td>
<td>-</td>
<td>Maintenance</td>
<td></td>
</tr>
</tbody>
</table>

BID=twice daily; BRCA=breast cancer susceptibility gene; CR/PR=complete response or partial response; EMA=European Medicine Agency; FDA=Food and Drug Administration; g/sBRCA=germline and/or somatic BRCA1/2 mutation; HGOC=high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer; HGSO=high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer; OC=epithelial ovarian, fallopian tube, or primary peritoneal cancer; QD=once daily.
Platinum-Sensitive BRCA mutated High Grade Serous Ovarian Cancer (study NCT02855697) is a phase I study that includes BRCA1/2 patients, and OREO (Olaparib Maintenance Treatment in Patients with Epithelial Ovarian Cancer) is a phase III study (NCT03106987) involving patients with and without BRCA mutations.

Platinum resistant recurrence

Platinum resistant EOC is defined as recurrence of disease within six months of completion of platinum and adjuvant chemotherapy. Platinum resistance generally portends a very poor prognosis, with overall survival rates from the time of diagnosis of resistant disease of only 12-14 months. Discussions about goals of care and quality of life, essential to any cancer discussion, are critical at this junction as this class of ovarian cancer is almost uniformly incurable. Surgery is almost always avoided in this patient population, although some exceptions may exist.

Monotherapy strategies

Monotherapy for platinum resistant disease achieves minimal responses of the order of 10-20%. Single agent therapy includes weekly paclitaxel with a response rate of up to a 21% in a phase II clinical trial, with minimal grade 3-4 side effects. Another phase III trial compared the use of topotecan with PLD every 28 days and found similar response rates and overall survival (up to 13 months) with less toxicity in the PLD arm.

Angiogenesis therapy

In an attempt to enhance these response rates, the addition of bevacizumab to these three agents (topotecan, taxol, and PLD) was examined in a large phase III trial, AURELIA. Nearly 400 patients were randomized to single agent therapy with the aforementioned drugs or doublet therapy with the addition of bevacizumab. Inclusion criteria were very specific to exclude previous anti-angiogenesis toxicity in the PLD arm. In an attempt to enhance these response rates, the addition of bevacizumab to these three agents (topotecan, taxol, and PLD) was examined in a large phase III trial, AURELIA. Nearly 400 patients were randomized to single agent therapy with the aforementioned drugs or doublet therapy with the addition of bevacizumab. Inclusion criteria were very specific to exclude previous anti-angiogenesis treatment, bowel obstruction, or more than two previous lines of treatment. Outcome showed improved an ORR of 31%, improved PFS (6.7 months), and generally good tolerability with the addition of bevacizumab. A subset analysis showed that weekly paclitaxel with bevacizumab (ORR 53%) may offer the best benefit compared with the other doublet regimens, although it requires weekly infusions. No overall survival advantage was seen with the addition of bevacizumab. Another regimen to consider is cisplatin/gemcitabine plus bevacizumab, which was examined in a phase II
A recent phase II trial of 38 patients has shown the efficacy of combining a PD-1 inhibitor, nivolumab, with bevacizumab and showed a 60% ORR in patients with platinum sensitive tumors and mean PFS of 12.1 months. Of note, a phase II study of nivolumab monotherapy found a 15% ORR in patients with platinum resistant disease, with a mean PFS of 3.5 months and overall survival of 20 months. Other combination immunotherapies such as nivolumab with the CTLA-4 targeted therapy ipilimumab have shown up to 31% ORR and a hazard ratio of 0.59 for PFS in patients with platinum sensitive, recurrent EOC.

Folate receptor antibody drug conjugates
Folate receptor antibody drug conjugates such as mirvetuxumab soravtansine are another potential avenue to therapy in patients with platinum resistant, recurrent ovarian cancer. This was explored in a phase IIIB trial of 66 patients treated with mirvetuxumab and bevacizumab. The objective response rate of 39% and mean PFS of 6.8 months showed substantial promise for the use of this doublet combination in a heavily pretreated recurrent population. Ocular side effects such as blurred vision as well as keratopathy must be managed by proactive mitigation strategies (for example, lubricating and steroid eye drops) and patients must be followed closely for long-term ocular sequelae.
Mismatch repair and microsatellite instability in ovarian cancers
Testing for microsatellite instability and defects in mismatch repair is increasingly being used to identify point mutations that may offer targeted therapies in ovarian cancer. Defects in mismatch repair substantially increase the risk of developing ovarian cancer as part of hereditary cancer syndromes such as hereditary non-polyposis colorectal cancer. Identification of these defects in ovarian cancer patients is important both for genetic testing of family members and for the use of novel therapies. New data suggest that mismatch repair deficient and microsatellite instability-H ovarian cancer tumors may predict responsiveness to anti-PDL-1 immunotherapy agents such as pembrolizumab. Use of molecular markers such as MSI-H and PDL-1 is thus important in the armamentarium of targeted therapies in ovarian cancer.

Chimeric antigen receptor therapy
CAR-T in EOC is a potentially novel way to fight metastatic ovarian cancer. CAR-T is a complicated and expensive process that has shown promise in killing cancer cells in a host of disease sites. It involves extraction of host T cells and use of gene editing to induce these cells to express chimeric antibodies on the cell surface, which then go and attach to cancer cells in the host when reintroduced. This type of therapy has shown promise mainly in blood malignancies, but a potentially significant application exists in solid tumors such as ovarian cancer. This is because ovarian cancer cells over-express MUC 16, which allows them to escape immune surveillance by host defense systems. A preliminary paper in Nature BME reported efficacy in tumor reduction in mouse models of ovarian cancer. Although these data are promising, CAR-T remains in its infancy for treatment of EOC.

Quality of life and palliative care
Providing comprehensive care is a commitment to recognizing that cancer care is a lifelong journey, exposing many patients to a multitude of relapses and treatment related adverse events that have the potential to negatively affect quality of life. The NCCN has guidelines to help oncology providers to optimize symptom management early in the disease process and feel comfortable discussing goals of care so that they align with the values, beliefs, and cultures of their patients as well as patients’ families and care givers. The goal of palliative care is to anticipate, prevent, and reduce suffering and to support the best possible quality of life, regardless of cancer stage or need for additional therapies. When integrated early, palliative care has been shown to have a profound effect on quality of life while reducing symptom intensity, particularly among patients with advanced cancer. Over the past 20 years, palliative care has developed into an integral part of comprehensive care, with the goal of early intervention to optimize quality of life with potential to improve survival outcomes as well. Importantly, this advancement in clinical care is equally matched by robust efforts in the research arena, as ongoing efforts are being made to integrate patient centered outcomes in clinical trial designs. Although palliative care should be started early in the disease process to optimize quality of life, we acknowledge that it becomes the primary focus of care when disease directed, life prolonging therapies are no longer effective or desired. Shared decision making between patients and oncologists is critical when selecting next treatment strategies, ensuring that these discussions include acceptable safety profile, balance symptom benefit with risks, and achieve a common goal.

Guidelines
The NCCN guidelines serve as internationally accepted standards to help to improve high quality, high value cancer care worldwide. The NCCN has an active presence in Europe, including more than 140,000 registered European users and almost 72,000 NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines) downloaded in 2018. The guidelines panel consists of members only from the US, but evidence based practices for ovarian cancer management stem from large, multicenter trials that have been conducted both in the US and internationally. Although NCCN guidelines are consistent with European Society for Medical Oncology guidelines, the section “Principles of systemic therapy” reflects specific therapeutic agents that are based on US FDA approval. Specific to the material covered in this review, we have highlighted some differences in indication and approval dates for PARP inhibitors.

The Journal of Clinical Oncology recently published a special issue devoted to summarizing the most important developments in treating gynecologic cancers. Invited authors included both US and internationally renowned oncologists who shared evidence based practices that have been widely adopted to achieve improved outcomes of women with gynecologic malignancies. We used this series of articles as a foundation for this review and made sure to site all relevant articles on ovarian cancer management.

Conclusions
EOC remains the most lethal gynecologic cancer, with most women presenting with advanced stage disease and five year survival rates approximating 48%. Surgical cytoreduction is a strong predictor of prognosis, as a direct correlation exists between the extent of postsurgical tumor residuum and progression-free and overall survival. PCS followed by platinum based chemotherapy remains the standard treatment for patients with advanced stage EOC, but neoadjuvant chemotherapy may
be considered for patients who are not likely to achieve optimal cytoreduction or who are poor surgical candidates. Research on first line treatment has focused on optimization of conventional chemotherapy with platinum/taxane doublet (for example, dose intensity, dose density, and incorporation of different agents, as well as intraperitoneal drug administration) and extended maintenance with cytotoxic chemotherapy during remission. Despite these advances, most patients with advanced stage disease experience relapse, and the likelihood of responding to subsequent courses of platinum based chemotherapy greatly depends on the platinum-free interval. Fortunately, advances in multiplex panels for cancer susceptibility for both germline and somatic mutations have led to several management strategies that have changed practice: universal genetic screening for all women with newly diagnosed EOC; targeted therapies such as bevacizumab and/or PARP inhibitors for first line maintenance therapy; and PARP inhibitor as monotherapy in the recurrent setting. Nevertheless, a greater understanding of the molecular landscape of EOC is needed to improve survival outcomes, especially for rare chemotherapy resistant histologies. Immediate research priorities should be aimed at developing robust clinical trials that test novel, targeted therapies that are supported by predictive biomarkers, integrate evaluation of mechanisms of sensitivity and resistance, and incorporate patient centered outcomes and quality of life measures.

QUESTIONs FOR FUTURE RESEARCH

• What are the biomarkers that predict improved treatment responses in advanced ovarian cancer (PD-L1, PD-1, CTLA-4, etc.)?
• What genetic aberrations occur to incite carcinogenesis in wild-type (non-BRCA mutated) ovarian cancer and how can these be detected earlier?
• Can the immune microenvironment be modulated to better potentiate treatments for ovarian cancer?

PATIENT INVOLVEMENT

A patient with advanced ovarian cancer, who is a PhD nurse scientist, assisted in answering questions about what issues are of concern to her as an ovarian cancer survivor. The patient raised issues revolving around palliative care and novel therapies

GLOSSARY OF ABBREVIATIONS

• ASCO—American Society of Clinical Oncology
• CA-125—cancer antigen 125
• CAR—chimeric antigen receptor therapy
• CTLA-4—cytotoxic T lymphocyte associated protein-4
• EMA—European Medicines Agency
• EOC—epithelial ovarian cancer
• EORTC—European Organization for Research and Treatment of Cancer
• FDA—Food and Drug Administration
• HGSOC—high grade serous ovarian cancer
• HiPEC—heated intraperitoneal chemotherapy
• HRD—homologous recombination deficiency
• ICS—interval cytoreductive surgery
• NCCN—National Comprehensive Cancer Network
• NBPC—non-platinum based chemotherapy
• ORR—overall response rate
• PARP—poly ADP-ribose polymerase
• PBC—platinum based chemotherapy
• PCS—primary cytoreductive surgery
• PD-1—programmed cell death 1
• PFI—platinum-free interval
• PFS—progression-free survival
• PLD—pegylated liposomal doxorubicin
• RFS—recurrence-free survival
• SGO—Society of Gynecologic Oncology
• VEGF—vascular endothelial growth factor

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