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# Treatment of epithelial ovarian cancer

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## 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.




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## 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*, *BPIP1*, *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.

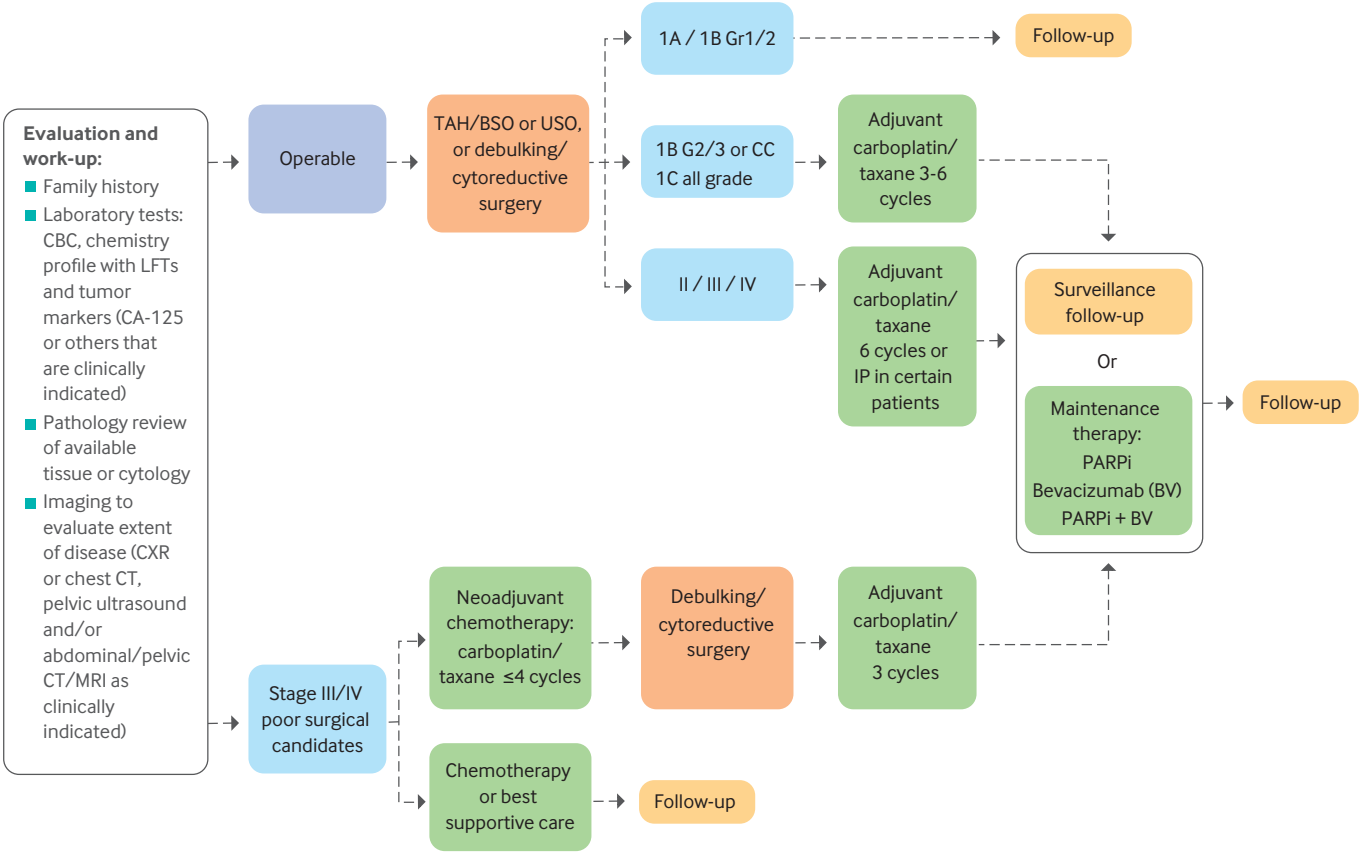


**Fig 1 | Evaluation and management of epithelial ovarian cancer. BSO=bilateral salpingo-oophorectomy; CA-125=cancer antigen 125; CBC=complete blood count; CT=computed tomography; CXR=chest ragiograph; LFT=liver function test; MRI=magnetic resonance imaging; PARPi=poly ADP-ribose polymerase inhibitor; TAH=total abdominal hysterectomy; USO=unilateral salpingo-oophorectomy.**





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## 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 IIIC or IV EOC should be evaluated by a gynecologic oncologist before treatment is started, to determine whether they are candidates for PCS.[19] 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).[19] 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.[20 21] 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 carcinoembryonic antigen ratio above 25 is acceptable to confirm the primary diagnosis and exclude a non-gynecologic cancer.[19] Should neoadjuvant chemotherapy be deemed the optimal management strategy, histological 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.[8 22-24] The American College of Surgeons and the American Geriatrics Society have provided general guidelines for the preoperative assessment of older patients undergoing surgery.[25] 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.[26]

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.[27 28] 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.[29]

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).[31-35] 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.[30] 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**

| Characteristics | High grade serous carcinoma | Clear cell carcinoma | Endometrioid carcinoma | Mucinous carcinoma | Low grade serous carcinoma |
|---|---|---|---|---|---|
| % of cases | 70 | 12 | 11 | 3 | 3 |
| Median age at diagnosis | 61 | 55 | 56 | 53 | 43 |
| Tumor marker(s) | CA-125 | CA-125 | CA-125 | CEA; CA19-9 | CA-125 |
| Genetic risk factors | BRCA1/2 | HNPCC | HNPCC/BRCA | Not known | Serous borderline tumor |
| Common stage at presentation | Advanced | Early | Early | Early | Advanced |
| Response to platinum based chemotherapy | Chemo-sensitive | Chemo-resistant radiosensitive | Chemo-sensitive | Chemo-resistant | Chemo-resistant |
| Common gene mutations | *P53*; *BRCA1/2*; HR defects | *PIK3CA*; *ARD1A*; *PTEN*; MSI | *CTNNB1*; *ARID1A*; *PTEN*; MSI | *KRAS*; *HER2*; *CDKN2A* | *BRAF*; *KRAS*; *NRAS*; *ERBB2*; *PIK3CA* |
| Common immune profile | P53+; WT1+; Pax8+; high Ki67 | HNF β+; WT1-; ER- | ER+; Pax8+; vimentin+ WT1-; P53 wild-type | CK20+; Cdx2+; CK7+; ER-; WT1- | WT1+; Pax8+; P53 wild-type; low Ki67 |

BRCA1/2=breast cancer susceptibility gene 1/2; CA-125=cancer antigen 125; CEA=carcinoembryonic antigen; ER=estrogen receptor; HNPCC=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.[34] Median overall survival was equivalent (29 *v* 30 months for neoadjuvant chemotherapy *v* 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.[33] 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=0.049).[34]

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.[34] 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.[36] Those with stage IIIC tumors smaller than 4.5 cm benefited more from PCS, whereas stage IV patients with metastatic tumors larger 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.[37-39] 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.[39]

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.[40] 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.[41]

### 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/

**Table 2 | Trials studying neoadjuvant chemotherapy versus primary cytoreductive surgery[30]**

| Study* | Inclusion criteria | Arms (n) | No residual disease | Grade 3-4 postoperative complication† | Progression-free survival (months) | Overall survival‡ (months) |
|---|---|---|---|---|---|---|
| SCORPION[31 32] | Stage IIIC-IV; Fagotti score 8-12 | NACT (55) *v* PCS (55) | 58% *v* 46%; P=0.16 | 6% *v* 53%; P=000001 | – | – |
| CHORUS[33] | Stage III-IV based on imaging or clinical evidence of pelvic mass with extra pelvic disease; CA-125/CEA >25 | NACT (274) *v* PCS (276) | 39% *v* 17%; P=0.0001 | 14% *v* 24%; P=0.007 | 12 *v* 10.7; HR 0.91 (95% CI 0.76 to 1.09) | 24.1 *v* 22.6; HR 0.87 (0.72 to 1.05) |
| EORTC 55971[34] | Biopsy proven stage IIIC-IV. In combination with pelvic mass, presence of metastasis of ≥2cm outside the pelvis, and CA-125/CEA ≥25 | NACT (334) *v* PCS (336) | 51% *v* 19% | Mortality: 0.7% *v* 0.6%; sepsis: 8% *v* 2%; hemorrhage: 7% *v* 4% | 12 *v* 12; HR 1.01 (0.89 to 1.15) | 30 *v* 29; HR 0.98 (0.84 to 1.13); P=0.01 |
| JCOG0602[35] | Stage III-IV based on CT, MRI, cytological tests, CA-125 >200 U/mL, and CEA <20 ng/mL | NACT (152) *v* PCS (149) | 63% *v* 30% | 5% *v* 15%; P=0.005 | - | 44.3 *v* 49.0; HR 1.05 (0.08 to 1.33); P=0.24 |

CA-125=cancer antigen 125; CEA=carcinoembryonic antigen; CT=computed tomography; HR=hazard ratio; MRI=magnetic resonance imaging; NACT=neoadjuvant chemotherapy; PCS=primary cytoreductive surgery.
*All were designed as non-inferiority trials except for SCORPION (superiority trial).
†Primary outcome for SCORPION.
‡Primary outcome for CHORUS, EORTC55971, and JCOG0602.

year).[42] 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.[43 44] 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.[40]

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.[45] 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.[46] 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/m$^2$) 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.[7] 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 HGSOC. 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 randomized trials, which showed that platinum based adjuvant chemotherapy, compared with observation, improved overall survival (hazard ratio 0.67, 0.5 to 0.9; P=0.008) and RFS (0.64, 0.5 to 0.82; P=0.001) among patients with surgically resected early stage EOC.[51] A subgroup analysis, which was likely to be limited by numbers, of the combined ICON1/ACTION data within the subcategories of age, stage, histology, and cell differentiation provided no evidence that the effect of chemotherapy was different within any of the subgroups.

Impact of surgical staging was assessable only in the ACTION trial, although only about a third of patients were fully staged. After a median follow-up of 5.5 years, the original ACTION trial results showed that the benefit of chemotherapy seemed to be limited to patients with non-optimal staging. Long term results after a median follow-up of 10.1 years supported most conclusions from the original analysis, with the exception that overall survival after optimal surgical staging was improved, even among patients who received adjuvant chemotherapy (hazard ratio of death 1.89, 0.99 to 3.60; P=0.05).[52] A meta-analysis of all randomized clinical trials comparing adjuvant chemotherapy with observation for patients with adequately staged I-II EOC showed no survival benefit of adjuvant chemotherapy (hazard ratio 0.91, 0.51 to 1.61).[53]

### Adjuvant therapy for advanced stage ovarian cancer patients

First line chemotherapy for EOC is a platinum agent with a taxane. GOG111, a landmark phase III trial, showed improved overall survival with the combination of cisplatin and paclitaxel compared with cisplatin and cyclophosphamide.[54] Other landmark trials that answered important clinical questions have shown that: carboplatin is as effective as cisplatin and better tolerated[55]; weekly dose-dense chemotherapy with carboplatin and paclitaxel compared with standard three weekly chemotherapy does not improve long term PFS[56]; adding a third drug to a doublet chemotherapy has no additional benefit[57-59]; extended cycles of chemotherapy do not confer survival benefit[60]; and, likewise, docetaxel-carboplatin seems to provides similar PFS and response to paclitaxel-carboplatin at the expense of more 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).[61]

### Intravenous versus intraperitoneal chemotherapy

In women with optimally cytoreduced, ideally to no gross residual, disease who have not received neoadjuvant 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 regimen[64] 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 (≥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$^2$). 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**

| | | Progression-free survival | | | Overall survival* | | |
|---|---|---|---|---|---|---|---|
| Study | Study groups | Length (months) | Effect size (95% CI) | P value | Length (months) | Effect size (95% CI) | P value |
| GOG 104[62] | Cisplatin 100 mg/m$^2$ IV; cyclophosphamide 600 mg/m$^2$ IV; Q3 wks × 6 cycles | NR | NR | NR | 41 | HR 0.76 (0.61 to 0.96) | 0.02 |
| | Cisplatin 100 mg/m$^2$ IP; cyclophosphamide IV; Q3 wks × 6 cycles | NR | | | 49 | | |
| GOG 114[63] | Cisplatin 100 mg/m$^2$ IV; cyclophosphamide 60 mg/m$^2$ IV; Q3 wks × 6 cycles | 22.2 | RR 0.78 (0.66 to 0.94) | 0.01 | 52.2 | RR 0.81 (0.65 to 1.00) | 0.05 |
| | Carboplatin (AUC 9) IV every 4 wks × 2; D1 taxol 135 mg/m$^2$ (24 h) IV; D2 cisplatin 100 mg/m$^2$ IP Q3 wks × 6 | 27.9 | | | 63.2 | | |
| GOG 172[64] | D1 taxol 135 mg/m$^2$ (24 h); D2 cisplatin 100 mg/m$^2$ IV | 18.3 | RR 0.80 (0.64 to 1.00) | 0.05 | 49.7 | RR 0.75 (0.58 to 0.97) | 0.03 |
| | D1 taxol 135 mg/m$^2$ (24 h); D2 cisplatin 75 mg/m$^2$ IV; D8 taxol 60 mg/m$^2$ IP | 23.8 | | | 65.6 | | |
| GOG 252[65] | Arm 1: taxol 80 mg/m$^2$ weekly IV; carboplatin AUC 6 IV; bev 15 mg/kg IV; bev maintenance × 15 cycles | 24.9 | Arm 1 *v* 2: HR 0.93 (0.80 to 1.07); arm 1 *v* 3: 0.98 (0.85 to 1.13) | NR | 75.5 | Arm 1 *v* 2: HR 0.95 (0.80 to 1.13); arm 1 *v* 3: 1.05 (0.88 to 1.24) | NR<br>NR |
| | Arm 2: taxol 80 mg/m$^2$ weekly IV; carboplatin AUC 6 IP; bev 15 mg/kg IV; bev maintenance × 15 cycles | 27.4 | | | 78.9 | | |
| | Arm 3: D1 taxol 135 mg/m$^2$ IV (24 h); D2 cisplatin 75 mg/m$^2$ IP; D8 taxol 60 mg/m$^2$ IP; bev 15 mg/kg IV; bev maintenance × 15 cycles | 26.2 | | | 72.9 | | |

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 crossover and insufficient power.

GOG175 was another trial that evaluated maintenance paclitaxel, but in an early staged population IA or IB (grade 3 or clear cell), all stage IC, and II EOC.[77] After completion of six cycles of carboplatin AUC6 and paclitaxel 175 mg/m$^2$ for three 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 up-front setting among patients with advanced EOC.[78 79] 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 *v* 16.6 months; hazard ratio for disease progression or death 0.59, 0.49 to 0.72; P<0.001).[81] This survival benefit also extended to patients with tumors showing HRD regardless of *BRCA* status.

Veliparib (VELIA trial; NCT02470585)[4] and niraparib (PRIMA trial; NCT02655016)[5] 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 *v* 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 *v* 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 *v* 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 exploiting 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 treatment following carboplatin/paclitaxel chemotherapy in 998 previously untreated patients with locally advanced or metastatic EOC. At the time of the planned interim analysis, an independent data monitoring panel determined that neither of the two avelumab arms would show a PFS benefit over the control arm of chemotherapy alone. The trial was terminated, but the investigation to determine the optimal approach to using immune checkpoint inhibitors in ovarian cancers is certainly at the forefront of research. Other important research considerations include what the optimal control arm is and whether using adaptive platform trial designs is feasible in EOC trials, whereby a single protocol simultaneously evaluates multiple treatments, dropping arms for futility, declaring superiority of one arm over another, or even adding new treatment arms as the trial progresses.[82]

### Surveillance

The SGO published a position statement for post-treatment surveillance with the goal of providing cost effective, evidence based strategies to optimize oncologic outcomes.[83] 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.[84] 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.[85] 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.[86]

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).[87] 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%)[88] or positron emission tomography (sensitivity 45-100%, specificity 40-100%).[88-90] Ultrasonography 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 trebectedin-PLD if the PFI were balanced between study arms. INOVATYON, 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

Table 4 | Landmark chemotherapy trials in platinum sensitive recurrent ovarian cancer

| Study | Primary outcome | Study groups | Progression-free survival | | | Overall survival | | |
|---|---|---|---|---|---|---|---|---|
| | | | Length (months) | Hazard ratio (95% CI) | P value | Length (months) | Hazard ratio (95% CI) | P value |
| ICON4[100] | OS | Carbo | 10 | 0.76 (0.66 to 0.89) | 0.0004 | 24 | 0.82 (0.69 to 0.97) | 0.02 |
| | | Carbo/taxol | 13 | | | 29 | | |
| AGO[101] | PFS | Carbo | 5.8 | 0.72 (0.58 to 0.90) | 0.003 | 17.3 | 0.96 (0.75 to 1.23) | 0.73 |
| | | Carbo/gem | 8.6 | | | 18.0 | | |
| CALYPSO[102] | PFS | Carbo/taxol | 9.4 | 0.82 (0.72 to 0.94) | 0.005 | 30.7 | 0.99 (0.85 to 1.16) | 0.94 |
| | | Carbo/PLD | 11.3 | | | 33.0 | | |
| OCEANS[103] | PFS | Carbo/gem/placebo | 8.4 | 0.48 (0.39 to 0.61) | <0.0001 | 32.9 | 0.95 (0.77 to 1.17) | 0.65 |
| | | Carbo/gem/bev | 12.4 | | | 33.6 | | |
| GOG 213[104]* | PFS | Carbo/taxol | 10.4 | 0.63 (0.53 to 0.74) | <0.001 | 37.3 | 0.83 (0.68 to 1.01) | 0.06 |
| | | Carbo/taxol/bev + bev maintenance | 13.8 | | | 42.2 | | |
| AGO-OVA 2.21/ ENGOT[105] | PFS | Carbo/gem/bev + bev maintenance | 11.7 | 0.80 (0.68 to 0.96) | 0.013 | NR | NR | NR |
| | | Carbo/PLD/bev + bev maintenance | 13.3 | | | NR | | |

bev=bevacizumab; Carbo=carboplatin; gem=gemcitabine; NR=not reported; PLD=pegylated liposomal doxorubicin.
*OS based on audited treatment-free interval stratification data: hazard ratio 0.823 (0.68 to 0.996); P=0.0447.

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).[101] 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

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 re-challenge 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.[109] 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.[6 110-112] 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.[111 112] 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 *v* 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 g*BRCA* 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 MOLTO (Multi-maintenance Olaparib After Disease Recurrence in Participants With

**Table 5 | Poly ADP-ribose polymerase (PARP) inhibitors for patients with epithelial ovarian cancer (EOC)**

| Drug | Time of approval | Agency | Indications | BRCA status | Clinical setting | Dosing |
|---|---|---|---|---|---|---|
| Olaparib | December 2018 | FDA | Advanced EOC, post CR/PR to platinum based chemotherapy | g/*sBRCA* | First line maintenance | 300 mg BID |
| | August 2017 | | Advanced EOC | *gBRCA* | Monotherapy, fourth line | |
| | | | Platinum sensitive recurrent OC, post CR/PR | - | Maintenance | |
| | February 2018 | EMA | Platinum sensitive recurrent HGOC, post CR/PR | - | Maintenance | |
| Rucaparib | December 2016 | FDA | Advanced OC | g/*sBRCA* | Monotherapy, third line | 600 mg BID |
| | April 2018 | | Platinum sensitive recurrent OC, post CR/PR | - | Maintenance | |
| | May 2018 | EMA | Platinum sensitive recurrent or progressive HGOC | g/*sBRCA* | Monotherapy, third line | |
| | Jan 2019 | | Platinum sensitive recurrent OC, post CR/PR | - | Maintenance | |
| Niraparib | March 2017 | FDA | Platinum sensitive recurrent OC, post CR/PR | - | Maintenance | 300 mg QD |
| | September 2017 | EMA | Platinum sensitive recurrent HGSOC, post CR/PR | - | Maintenance | |

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; HGSOC=high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer; OC=epithelial ovarian, fallopian tube, or primary peritoneal cancer; QD=once daily.

**Table 6 | Poly ADP-ribose polymerase (PARP) inhibitor maintenance for patients with platinum sensitive, recurrent ovarian cancer**

| | Olaparib | | Rucaparib | Niraparib |
|---|---|---|---|---|
| | STUDY19[6] | SOLO2[110] | ARIEL3[111] | NOVA[112] |
| **Design** | | | | |
| No of patients | 265 | 295 | 564 | 553 |
| Population | Platinum sensitive recurrent HGSOC; PR/CR after ≥2 previous lines of PBC | Platinum sensitive recurrent HGS or endometrioid OC; PR/CR after ≥2 previous lines of PBC | Platinum sensitive recurrent HGS or endometrioid OC; PR/CR after ≥2 previous lines of PBC ≥2 previous lines of PBC | Platinum sensitive HGSOC; PR/CR after ≥2 previous lines of PBC |
| Eligible *BRCA* status | g*BRCA*; s*BRCA*; BRCAwt | g*BRCA*; s*BRCA* | g*BRCA*; s*BRCA*; *BRCA*wt | g*BRCA*; s*BRCA*; *BRCAwt* |
| HRD assessment | - | - | FoundationFocus CDxBRCA LOH | myChoice HRD |
| Randomization | 1:1 | 2:1 | 2:1 | 2:1 |
| Intervention | Olaparib 400 mg BID (capsules) *v* placebo | Olaparib 300 mg BID (tablets) *v* placebo | Rucaparib 600 mg BID *v* placebo | Niraparib 300 mg daily *v* placebo |
| Primary endpoint | Investigator assessed PFS | Investigator assessed PFS | Investigator assessed PFS | Investigator assessed PFS and PFS by BICR |
| QOL assessment | FACT-O; FOSI | FACT-O; EQ-5D-5L | NFOSI-18; DRS-P | FOSI; EQ-5D-5L |
| **Results** | | | | |
| PFS g/*sBRCA*m | - | 19.1 *v* 5.5 months; HR 0.30 (95% CI 0.22 to 0.41); P<0.001 | 16.6 *v*.5.4 months; HR 0.23 (0.16 to 0.34); P<0.001 | 21.0 *v*. 5.5 months; HR 0.27 (0.17 to 0.41); P<0.001 |
| PFS g*BRCA*wt | - | 7.4 *v* 5.5 months; HR 0.54 (0.34 to 0.85); P=0.0075 | - | 9.3 *v* 3.9 months; 0.45 (0.34 to 0.61); <0.001 |
| PFS HRD or LOH high | - | NA | 9.7 *v* 5.4 months*; HR 0.44 (0.29 to 0.66); P<0.001 | 12.9 *v* 3.8 months; HR 0.38 (0.24 to 0.59);P<0.001 |
| PFS HRP or LOH low | - | NA | 6.7 *v* 5.4 months*; HR 0.58 (0.40 to 0.85); P=0.0049 | 6.9 *v* 3.8 months; HR 0.58 (0.36 to 0.92); P=0.02 |
| **Toxicities (%)** | | | | |
| Dose reduction | - | 25 | 55 | 66 |
| Drug discontinued | - | 11 | 13 | 14 |
| Any grade >3 AE* | - | 36 | 36 | 36 |
| Anemia | - | 25 | 19 | 25 |
| Neutropenia | - | 20 | 7 | 20 |
| Thrombocytopenia | - | 34 | 5 | 34 |
| Nausea | - | 3 | 4 | 3 |
| Fatigue | - | 8 | 7 | 8 |

AE=adverse event; BICR=blinded independent central review; BID=twice daily; *BRCA*=breast cancer susceptibility gene; *BRCAwt=BRCA* wild-type; *g/sBRCAm*=germline and/or somatic *BRCA1/2* mutation; DRS-P=disease related symptoms-physical; FACT-O=Functional Assessment of Cancer Therapy-Ovarian; FOSI=FACT/NCCN Ovarian Symptom Index; HR=hazard ratio; HRD=homologous recombination deficient/deficiency; HGS=high grade serious; HRP=homologous recombination proficient LOH=loss of heterozygosity; NFOSI-18=NCCN/FACT Ovarian Symptom Index (subset of FACT-O); OC=epithelial ovarian, fallopian tube, or primary peritoneal cancer; mo= months; PBC=platinum based chemotherapy; PFS=progression-free survival; QD=once daily; QOL=quality of life.
*Exploratory subgroup analyses.

Platinum-Sensitive *BRCA* mutated High Grade Serous Ovarian Cancer) study (NCT02855697) is a phase I study that includes *BRCA*1/2 patients, and OREO (Olaparib Maintenance Retreatment 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 surgery 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.[115] 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.[116 117]

#### *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 treatment, bowel obstruction, or more than two previous lines of treatment. Outcomes 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

clinical trial of both platinum resistant and platinum sensitive patients (n=35).[118] Interestingly, although numbers were small, a 78% complete and partial response rate was seen although 29% experienced grade 3-4 neutropenia. Given the incurable nature of this disease, management options for most patients are often based on ongoing toxicities and the potential impact of future treatments on quality of life. Incorporation of bevacizumab is a reasonable option on the basis of the AURELIA trial, knowing that the ideal candidate is one who has received fewer than two previous regimens, has no previous exposure to bevacizumab, and has no history of a bowel obstruction in the previous six months (or no evidence of malignant bowel involvement).

The use of immunotherapy (discussed in detail below) and PARP therapy presents a potential new frontier in the treatment of platinum resistant EOC. The results of the phase II TOPACIO/KEYNOTE-162 trial showed that 300 mg of daily niraparib orally with 200 mg of intravenous pembrolizumab every 21 days had a 13% and 47% partial and stable response rate, respectively.[119] The disease control rate of 65% was impressive in this cohort of platinum resistant patients. The QUADRA study evaluated the efficacy of single agent niraparib at 300 mg daily in a heavily pretreated group (three or more previous lines of chemotherapy) of patients with recurrent EOC.[120] A total of 463 patients were enrolled, of whom 151 (33%) had platinum resistant disease and 161 (35%) were refractory to platinum. ORR was as high as 28%, with a low complication rate globally. Given that quality of life is of paramount importance, the use of an oral agent to obtain treatment response is important in this group.

Another notable trial for this specific population is the randomized, open label, phase III JAVELIN Ovarian 200 trial presented at the 2019 SGO Annual Meeting on Women's Cancer. Avelumab alone or in combination with pegylated liposomal doxorubicin did not meet its primary objectives of significantly improving PFS or overall survival among patients with platinum resistant or refractory EOC. However, the planned subgroup analysis suggested that patients with PD-L1 positive tumors (58% of patients) had improved PFS (3.7 *v* 1.9 months) and improved overall survival (18.4 *v* 13.8 months) for avelumab-PLD versus PLD.

## Emerging and novel therapies

### Immunotherapy

Immunotherapy presents a potentially novel frontier in the treatment of recurrent EOC. Immune checkpoints are regulators of the immune system, intended to maintain self-tolerance and prevent autoimmunity. However, some cancers can protect themselves from immune attack by stimulating immune checkpoint targets. Studies have shown the efficacy of immune based therapies with improved survival in a host of cancers including metastatic melanoma, renal cell carcinoma, and lung cancer.[121-123] In particular, the association of intratumoral tumor infiltrating lymphocytes and improved clinical outcomes for EOC patients suggests that this tumor type is potentially immunoreactive, but preliminary trials have shown mixed results with regard to the efficacy of these modalities.

Given that this is an evolving area of active research, we highlight here only a few studies involving the combination of checkpoint inhibitors with PARP inhibitors, bevacizumab, or both. The basis of studying such combinations stems from mouse models that have shown that PARP inhibitors can activate interferon signaling and synergize with programmed cell death 1 (PD-1) or cytotoxic T lymphocyte associated protein-4 (CTLA-4) blockade.[124] Translating this to early phase clinical trials, the MEDIOLA study was presented as a late breaking abstract at SGO 2018. It was an open label, phase II basket study of durvalumab (anti-PD-L1) in combination with olaparib, studied in 32 patients with platinum sensitive recurrent *BRCA* mutated tumors and resulted in an ORR of 72%, including a complete response rate of 19%.[125] Among patients with *BRCA* wild-type tumors, the combination resulted in an ORR of 17% and a disease control rate of 83% at six months. Overall, it was well tolerated, although the most frequent grade 3 or higher adverse events were anemia (12%) and increased lipase (9%); the most common immune related adverse events (all grades) were hypothyroidism (15%) and rash (12%). As mentioned above, results from the phase I/II TOPACIO/KEYNOTE-162 trial confirmed tolerability and antitumor activity in recurrent EOC patients with the combination of the PARP inhibitor niraparib with an anti-PD-1 antibody, pembrolizumab.[119]

A recent phase II trial of 38 patients has shown the efficacy of combining a PD-1 inhibitor, nivolumab, with bevacizumab and showed a 40% ORR in patients with platinum sensitive tumors and mean PFS of 12.1 months.[126] 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.[127] 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.[128]

### 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 IB trial of 66 patients treated with mirvetuxumab and bevacizumab.[129] 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.[130] The KEYNOTE-028 trial showed that in a subset of PDL-1 positive patients with EOC, pembrolizumab conferred durable antitumor activity with manageable safety and toxicity.[131] 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.[132] Although these data are promising, CAR-T remains in its infancy for treatment of EOC.

## Quality of life and palliative care

Providing comprehensive cancer 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.[133] 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.[134] 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.[135 136] 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 720 000 NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines) downloaded in 2018.[137] 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.[138] 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%.[2] 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.[38 39] 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.[30] 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,[139] and incorporate patient centered outcomes and quality of life measures.

### GLOSSARY OF ABBREVIATIONS

- ASCO—American Society of Clinical Oncology
- CA-125—cancer antigen 125
- CAR-T—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
- NPBC—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

### 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

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1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7-30. doi:10.3322/caac.21590
2 National Cancer Institute. Cancer Stat Facts: Ovarian Cancer. https://seer.cancer.gov/statfacts/html/ovary.html.
3 Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med* 2018;379:2495-505. doi:10.1056/NEJMoa1810858
4 Coleman RL, Fleming GF, Brady MF, et al. Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. *N Engl J Med* 2019;381:2403-15. doi:10.1056/NEJMoa1909707
5 González-Martín A, Pothuri B, Vergote I, et al, PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med* 2019;381:2391-402. doi:10.1056/NEJMoa1910962
6 Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012;366:1382-92. doi:10.1056/NEJMoa1105535
7 van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. *N Engl J Med* 2018;378:230-40. doi:10.1056/NEJMoa1708618
8 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Older Adult Oncology. Version 1. 2020. https://www.nccn.org/professionals/physician_gls/pdf/senior.pdf.
9 Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C, ESMO Guidelines Working Group. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24(Suppl 6):vi24-32. doi:10.1093/annonc/mdt333
10 International Agency for Research on Cancer. Estimated number of incident cases from 2018 to 2040 ovary, females all ages. 2018. https://gco.iarc.fr/tomorrow/graphic-isotype?type=0&population=900&mode=population&sex=2&cancer=39&age_group=value&apc_male=0&apc_female=0.
11 Kuchenbaecker KB, Hopper JL, Barnes DR, et al, BRCA1 and BRCA2 Cohort Consortium. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA* 2017;317:2402-16. doi:10.1001/jama.2017.7112
12 Norquist BM, Harrell MI, Brady MF, et al. Inherited Mutations in Women With Ovarian Carcinoma. *JAMA Oncol* 2016;2:482-90. doi:10.1001/jamaoncol.2015.5495
13 Frey MK, Pothuri B. Homologous recombination deficiency (HRD) testing in ovarian cancer clinical practice: a review of the literature. *Gynecol Oncol Res Pract* 2017;4:4. doi:10.1186/s40661-017-0039-8

14 Pennington KP, Swisher EM. Hereditary ovarian cancer: beyond the usual suspects. *Gynecol Oncol* 2012;124:347-53. doi:10.1016/j.ygyno.2011.12.415
15 Finch A, Beiner M, Lubinski J, et al, Hereditary Ovarian Cancer Clinical Study Group. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. *JAMA* 2006;296:185-92. doi:10.1001/jama.296.2.185
16 Shulman LP. Hereditary breast and ovarian cancer (HBOC): clinical features and counseling for BRCA1 and BRCA2, Lynch syndrome, Cowden syndrome, and Li-Fraumeni syndrome. *Obstet Gynecol Clin North Am* 2010;37:109-33. doi:10.1016/j.ogc.2010.03.003
17 Stan DL, Shuster LT, Wick MJ, Swanson CL, Pruthi S, Bakkum-Gamez JN. Challenging and complex decisions in the management of the BRCA mutation carrier. *J Womens Health (Larchmt)* 2013;22:825-34. doi:10.1089/jwh.2013.4407
18 Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011;474:609-15. doi:10.1038/nature10166
19 Wright AA, Bohlke K, Armstrong DK, et al. Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2016;34:3460-73. doi:10.1200/JCO.2016.68.6907
20 Covens AL. A critique of surgical cytoreduction in advanced ovarian cancer. *Gynecol Oncol* 2000;78:269-74. doi:10.1006/gyno.2000.5926
21 Rauh-Hain JA, Nitschmann CC, Worley MJJr, et al. Platinum resistance after neoadjuvant chemotherapy compared to primary surgery in patients with advanced epithelial ovarian carcinoma. *Gynecol Oncol* 2013;129:63-8. doi:10.1016/j.ygyno.2013.01.009
22 Fukuse T, Satoda N, Hijiya K, Fujinaga T. Importance of a comprehensive geriatric assessment in prediction of complications following thoracic surgery in elderly patients. *Chest* 2005;127:886-91. doi:10.1378/chest.127.3.886
23 Audisio RA, Pope D, Ramesh HS, et al, PACE participants. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. *Crit Rev Oncol Hematol* 2008;65:156-63. doi:10.1016/j.critrevonc.2007.11.001
24 Robinson TN, Eiseman B, Wallace JI, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. *Ann Surg* 2009;250:449-55.
25 Chow WB, Rosenthal RA, Merkow RP, Ko CY, Esnaola NF, American College of Surgeons National Surgical Quality Improvement Program, American Geriatrics Society. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. *J Am Coll Surg* 2012;215:453-66. doi:10.1016/j.jamcollsurg.2012.06.017
26 Thrall MM, Goff BA, Symons RG, Flum DR, Gray HJ. Thirty-day mortality after primary cytoreductive surgery for advanced ovarian cancer in the elderly. *Obstet Gynecol* 2011;118:537-47. doi:10.1097/AOG.0b013e31822a6d56
27 Fagotti A, Ferrandina G, Fanfani F, et al. Prospective validation of a laparoscopic predictive model for optimal cytoreduction in advanced ovarian carcinoma. *Am J Obstet Gynecol* 2008;199:642. doi:10.1016/j.ajog.2008.06.052
28 Brun JL, Rouzier R, Uzan S, Daraï E. External validation of a laparoscopic-based score to evaluate resectability of advanced ovarian cancers: clues for a simplified score. *Gynecol Oncol* 2008;110:354-9. doi:10.1016/j.ygyno.2008.04.042
29 Gómez-Hidalgo NR, Martinez-Cannon BA, Nick AM, et al. Predictors of optimal cytoreduction in patients with newly diagnosed advanced-stage epithelial ovarian cancer: Time to incorporate laparoscopic assessment into the standard of care. *Gynecol Oncol* 2015;137:553-8. doi:10.1016/j.ygyno.2015.03.049
30 Wright AA, Bohlke K, Armstrong DK, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. *Gynecol Oncol* 2016;143:3-15. doi:10.1016/j.ygyno.2016.05.022
31 Fagotti A, Ferrandina G, Vizzielli G, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of peri-operative outcome. *Eur J Cancer* 2016;59:22-33. doi:10.1016/j.ejca.2016.01.017
32 Fagotti A, Vizzielli G, Ferrandina G, et al. Survival analyses from a randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer with high tumor load (SCORPION trial). *J Clin Oncol* 2018;36(15_suppl):5516. doi:10.1200/JCO.2018.36.15_suppl.5516
33 Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet* 2015;386:249-57. doi:10.1016/S0140-6736(14)62223-6
34 Vergote I, Coens C, Nankivell M, et al, EORTC, MRC CHORUS study investigators. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. *Lancet Oncol* 2018;19:1680-7. doi:10.1016/S1470-2045(18)30566-7
35 Onda T, Satoh T, Saito T, et al, Japan Clinical Oncology Group. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602. *Eur J Cancer* 2016;64:22-31. doi:10.1016/j.ejca.2016.05.017
36 van Meurs HS, Tajik P, Hof MH, et al. Which patients benefit most from primary surgery or neoadjuvant chemotherapy in stage IIIC or IV ovarian cancer? An exploratory analysis of the European Organisation for Research and Treatment of Cancer 55971 randomised trial. *Eur J Cancer* 2013;49:3191-201. doi:10.1016/j.ejca.2013.06.013
37 Elattar A, Bryant A, Winter-Roach BA, Hatem M, Naik R. Optimal primary surgical treatment for advanced epithelial ovarian cancer. *Cochrane Database Syst Rev* 2011;(8):CD007565. doi:10.1002/14651858.CD007565.pub2
38 Chang SJ, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. *Gynecol Oncol* 2013;130:493-8. doi:10.1016/j.ygyno.2013.05.040
39 Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002;20:1248-59. doi:10.1200/JCO.2002.20.5.1248
40 Bristow RE, Montz FJ, Lagasse LD, Leuchter RS, Karlan BY. Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. *Gynecol Oncol* 1999;72:278-87. doi:10.1006/gyno.1998.5145
41 Food and Drug Administration. Highlights of Prescribing Information: AVASTIN® (bevacizumab). 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf.
42 Bristow RE, Chang J, Ziogas A, Randall LM, Anton-Culver H. High-volume ovarian cancer care: survival impact and disparities in access for advanced-stage disease. *Gynecol Oncol* 2014;132:403-10. doi:10.1016/j.ygyno.2013.12.017
43 Melamed A, Rauh-Hain JA. Minimally invasive interval cytoreductive surgery: it's time for a randomized trial. *Int J Gynecol Cancer* 2019;29:1339-40. doi:10.1136/ijgc-2019-000971
44 Rauh-Hain J, Melamed A, Fagotti A, et al. LANCE Trial (Laparoscopic cytoreduction After Neoadjuvant Chemotherpy). 2020. https://gcigtrials.org/system/files/Lance%20trial.pdf.
45 Panici PB, Maggioni A, Hacker N, et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. *J Natl Cancer Inst* 2005;97:560-6. doi:10.1093/jnci/dji102
46 Harter P, Sehouli J, Lorusso D, et al. A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms. *N Engl J Med* 2019;380:822-32. doi:10.1056/NEJMoa1808424
47 Young RC, Walton LA, Ellenberg SS, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer. Results of two prospective randomized trials. *N Engl J Med* 1990;322:1021-7. doi:10.1056/NEJM199004123221501
48 Winter-Roach BA, Kitchener HC, Dickinson HO. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. *Cochrane Database Syst Rev* 2009;(3):CD004706. doi:10.1002/14651858.CD004706.pub3
49 Bell J, Brady MF, Young RC, et al, Gynecologic Oncology Group. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2006;102:432-9. doi:10.1016/j.ygyno.2006.06.013
50 Chan JK, Tian C, Fleming GF, et al. The potential benefit of 6 vs. 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study. *Gynecol Oncol* 2010;116:301-6. doi:10.1016/j.ygyno.2009.10.073
51 Trimbos JB, Vergote I, Bolis G, et al, EORTC-ACTION collaborators. European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. *J Natl Cancer Inst* 2003;95:113-25. doi:10.1093/jnci/95.2.113
52 Trimbos B, Timmers P, Pecorelli S, et al. Surgical staging and treatment of early ovarian cancer: long-term analysis from a randomized trial. *J Natl Cancer Inst* 2010;102:982-7. doi:10.1093/jnci/djq149
53 Tropé C, Kaern J. Adjuvant chemotherapy for early-stage ovarian cancer: review of the literature. *J Clin Oncol* 2007;25:2909-20. doi:10.1200/JCO.2007.11.1013
54 McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with

stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1-6. doi:10.1056/NEJM199601043340101
55 Ozols RF, Bundy BN, Greer BE, et al, Gynecologic Oncology Group. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2003;21:3194-200. doi:10.1200/JCO.2003.02.153
56 Clamp AR, James EC, McNeish IA, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. *Lancet* 2019;394:2084-95. doi:10.1016/S0140-6736(19)32259-7
57 Bolis G, Scarfone G, Raspagliesi F, et al. Paclitaxel/carboplatin versus topotecan/paclitaxel/carboplatin in patients with FIGO suboptimally resected stage III-IV epithelial ovarian cancer a multicenter, randomized study. *Eur J Cancer* 2010;46:2905-12. doi:10.1016/j.ejca.2010.06.124
58 du Bois A, Floquet A, Kim JW, et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. *J Clin Oncol* 2014;32:3374-82. doi:10.1200/JCO.2014.55.7348
59 Bookman MA. GOG0182-ICON5: 5-arm phase III randomized trial of paclitaxel (P) and carboplatin (C) vs combinations with gemcitabine (G), PEG-lipososomal doxorubicin (D), or topotecan (T) in patients (pts) with advanced-stage epithelial ovarian (EOC) or primary peritoneal (PPC) carcinoma. *J Clin Oncol* 2006;24(18_suppl):5002. doi:10.1200/jco.2006.24.18_suppl.5002
60 Dizon DS, Weitzen S, Rojan A, et al. Two for good measure: six versus eight cycles of carboplatin and paclitaxel as adjuvant treatment for epithelial ovarian cancer. *Gynecol Oncol* 2006;100:417-21. doi:10.1016/j.ygyno.2005.10.031
61 Vasey PA, Jayson GC, Gordon A, et al, Scottish Gynaecological Cancer Trials Group. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* 2004;96:1682-91. doi:10.1093/jnci/djh323
62 Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996;335:1950-5. doi:10.1056/NEJM199612263352603
63 Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol* 2001;19:1001-7. doi:10.1200/JCO.2001.19.4.1001
64 Armstrong DK, Bundy B, Wenzel L, et al, Gynecologic Oncology Group. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006;354:34-43. doi:10.1056/NEJMoa052985
65 Walker JL, Brady MF, Wenzel L, et al. Randomized Trial of Intravenous Versus Intraperitoneal Chemotherapy Plus Bevacizumab in Advanced Ovarian Carcinoma: An NRG Oncology/Gynecologic Oncology Group Study. *J Clin Oncol* 2019;37:1380-90. doi:10.1200/JCO.18.01568
66 Tewari D, Java JJ, Salani R, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: a gynecologic oncology group study. *J Clin Oncol* 2015;33:1460-6. doi:10.1200/JCO.2014.55.9898
67 Monk BJ, Chan JK. Is intraperitoneal chemotherapy still an acceptable option in primary adjuvant chemotherapy for advanced ovarian cancer?*Ann Oncol* 2017;28(suppl_8):i40, i45. doi:10.1093/annonc/mdx451
68 Wenzel LB, Huang HQ, Armstrong DK, Walker JL, Cella D, Gynecologic Oncology Group. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 2007;25:437-43. doi:10.1200/JCO.2006.07.3494
69 Katsumata N, Yasuda M, Isonishi S, et al, Japanese Gynecologic Oncology Group. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *Lancet Oncol* 2013;14:1020-6. doi:10.1016/S1470-2045(13)70363-2
70 Chan JK, Brady MF, Monk BJ. Weekly vs. Every-3-Week Paclitaxel for Ovarian Cancer. *N Engl J Med* 2016;374:2603-4. doi:10.1056/NEJMoa1505067
71 Clamp AR, James EC, McNeish IA, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. *Lancet* 2019;394:2084-95. doi:10.1016/S0140-6736(19)32259-7
72 Falandry C, Savoye AM, Stefani L, et al. EWOC-1: A randomized trial to evaluate the feasibility of three different first-line chemotherapy regimens for vulnerable elderly women with ovarian cancer (OC): A GCIG-ENGOT-GINECO study. *J Clin Oncol* 2019;37(15_suppl):5508. doi:10.1200/JCO.2019.37.15_suppl.5508
73 von Gruenigen VE, Huang HQ, Beumer JH, et al. Chemotherapy completion in elderly women with ovarian, primary peritoneal or fallopian tube cancer - An NRG oncology/Gynecologic Oncology Group study. *Gynecol Oncol* 2017;144:459-67. doi:10.1016/j.ygyno.2016.11.033
74 Pignata S, Di Maio M, Gallo C, Perrone F. Carboplatin plus paclitaxel scheduling for advanced ovarian cancer - authors' reply. *Lancet Oncol* 2014;15:e250-1. doi:10.1016/S1470-2045(14)70219-0
75 Markman M, Liu PY, Wilczynski S, et al, Southwest Oncology Group, Gynecologic Oncology Group. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. *J Clin Oncol* 2003;21:2460-5. doi:10.1200/JCO.2003.07.013
76 Markman M, Liu PY, Moon J, et al. Impact on survival of 12 versus 3 monthly cycles of paclitaxel (175 mg/m2) administered to patients with advanced ovarian cancer who attained a complete response to primary platinum-paclitaxel: follow-up of a Southwest Oncology Group and Gynecologic Oncology Group phase 3 trial. *Gynecol Oncol* 2009;114:195-8. doi:10.1016/j.ygyno.2009.04.012
77 Mannel RS, Brady MF, Kohn EC, et al. A randomized phase III trial of IV carboplatin and paclitaxel × 3 courses followed by observation versus weekly maintenance low-dose paclitaxel in patients with early-stage ovarian carcinoma: a Gynecologic Oncology Group Study. *Gynecol Oncol* 2011;122:89-94. doi:10.1016/j.ygyno.2011.03.013
78 Oza AM, Cook AD, Pfisterer J, et al, ICON7 trial investigators. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015;16:928-36. doi:10.1016/S1470-2045(15)00086-8
79 Tewari KS, Burger RA, Enserro D, et al. Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. *J Clin Oncol* 2019;37:2317-28. doi:10.1200/JCO.19.01009
80 Ferriss JS, Java JJ, Bookman MA, et al. Ascites predicts treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian, fallopian tube and peritoneal cancers: an NRG Oncology/GOG study. *Gynecol Oncol* 2015;139:17-22. doi:10.1016/j.ygyno.2015.07.103
81 Ray-Coquard I, Pautier P, Pignata S, et al, PAOLA-1 Investigators. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *N Engl J Med* 2019;381:2416-28. doi:10.1056/NEJMoa1911361
82 Saville BR, Berry SM. Efficiencies of platform clinical trials: A vision of the future. *Clin Trials* 2016;13:358-66. doi:10.1177/1740774515626362
83 Salani R, Khanna N, Frimer M, Bristow RE, Chen LM. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. *Gynecol Oncol* 2017;146:3-10. doi:10.1016/j.ygyno.2017.03.022
84 Miller RE, Rustin GJ. How to follow-up patients with epithelial ovarian cancer. *Curr Opin Oncol* 2010;22:498-502. doi:10.1097/CCO.0b013e32833ae8b6
85 Rustin GJ, van der Burg ME. A randomized trial in ovarian cancer (OC) of early treatment of relapse based on CA125 level alone versus delayed treatment based on conventional clinical indicators (MRC OV05/EORTC 55955 trials). *J Clin Oncol* 2009;27(15_suppl):1. doi:10.1200/jco.2009.27.15_suppl.1 .
86 Lindemann K, Kristensen G, Mirza MR, et al. Poor concordance between CA-125 and RECIST at the time of disease progression in patients with platinum-resistant ovarian cancer: analysis of the AURELIA trial. *Ann Oncol* 2016;27:1505-10. doi:10.1093/annonc/mdw238
87 Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. *Am J Obstet Gynecol* 2011;204:466-78. doi:10.1016/j.ajog.2011.03.008
88 Gadducci A, Cosio S. Surveillance of patients after initial treatment of ovarian cancer. *Crit Rev Oncol Hematol* 2009;71:43-52. doi:10.1016/j.critrevonc.2008.12.008
89 Gu P, Pan LL, Wu SQ, Sun L, Huang G. CA 125, PET alone, PET-CT, CT and MRI in diagnosing recurrent ovarian carcinoma: a systematic review and meta-analysis. *Eur J Radiol* 2009;71:164-74. doi:10.1016/j.ejrad.2008.02.019
90 Vaidya AP, Curtin JP. The follow-up of ovarian cancer. *Semin Oncol* 2003;30:401-12. doi:10.1016/S0093-7754(03)00100-3
91 Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian

cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol* 2009;27:1419-25. doi:10.1200/JCO.2008.19.1684
92 Luvero D, Milani A, Ledermann JA. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. *Ther Adv Med Oncol* 2014;6:229-39. doi:10.1177/1758834014544121
93 Gore ME, Fryatt I, Wiltshaw E, Dawson T. Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. *Gynecol Oncol* 1990;36:207-11. doi:10.1016/0090-8258(90)90174-J
94 Poveda A, Vergote I, Tjulandin S, et al. Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer: outcomes in the partially platinum-sensitive (platinum-free interval 6-12 months) subpopulation of OVA-301 phase III randomized trial. *Ann Oncol* 2011;22:39-48. doi:10.1093/annonc/mdq352
95 Kaye SB, Colombo N, Monk BJ, et al. Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer delays third-line chemotherapy and prolongs the platinum-free interval. *Ann Oncol* 2011;22:49-58. doi:10.1093/annonc/mdq353
96 Monk BJ, Herzog TJ, Kaye SB, et al. Trabectedin plus pegylated liposomal doxorubicin (PLD) versus PLD in recurrent ovarian cancer: overall survival analysis. *Eur J Cancer* 2012;48:2361-8. doi:10.1016/j.ejca.2012.04.001
97 Pignata S, Scambia G, Bologna A, et al. Randomized Controlled Trial Testing the Efficacy of Platinum-Free Interval Prolongation in Advanced Ovarian Cancer: The MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG Study. *J Clin Oncol* 2017;35:3347-53. doi:10.1200/JCO.2017.73.4293
98 Coleman RL, Enserro D, Spirtos N, et al. A phase III randomized controlled trial of secondary surgical cytoreduction (SSC) followed by platinum-based combination chemotherapy (PBC), with or without bevacizumab (B) in platinum-sensitive, recurrent ovarian cancer (PSOC): A NRG Oncology/Gynecologic Oncology Group (GOG) study. *J Clin Oncol* 2018;36(15_suppl):5501. doi:10.1200/JCO.2018.36.15_suppl.5501
99 Bois AD, Vergote I, Ferron G, et al. Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20. *J Clin Oncol* 2017;35(15_suppl):5501. doi:10.1200/JCO.2017.35.15_suppl.5501
100 Parmar MK, Ledermann JA, Colombo N, et al, ICON and AGO Collaborators. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003;361:2099-106. doi:10.1016/S0140-6736(03)13718-X
101 Pfisterer J, Plante M, Vergote I, et al, AGO-OVAR, NCIC CTG, EORTC GCG. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006;24:4699-707. doi:10.1200/JCO.2006.06.0913
102 Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol* 2010;28:3323-9. doi:10.1200/JCO.2009.25.7519
103 Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012;30:2039-45. doi:10.1200/JCO.2012.42.0505
104 Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017;18:779-91. doi:10.1016/S1470-2045(17)30279-6
105 Pfisterer J DA, Baumann K, Rau J, Harter P, Joly F, Sehouli J, Canzler U, Schmalfeldt B, Shannon C, Hein A, Reimer D, Hanker L, Petit T, Marmé F, El-Balat A, Glasspool R, de Gregorio N, Mahner S, Kurtz J.Carboplatin/pegylated liposomal doxorubicin/bevacizumab (CD-BEV) vs. carboplatin/gemcitabine/bevacizumab (CG-BEV) in patients with recurrent ovarian cancer. A prospective randomized phase III ENGOT/GCIG-INTERGROUP STUDY (AGO STUDY GROUP, AGO-AUSTRIA, ANZGOG, GINECO, SGCTG). *Ann Oncol* 2018;29(suppl 8):viii332-58. doi:10.1093/annonc/mdy285.142
106 Raja FA, Counsell N, Colombo N, et al. Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data. *Ann Oncol* 2013;24:3028-34. doi:10.1093/annonc/mdt406
107 Wagner U, Marth C, Largillier R, et al. Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients. *Br J Cancer* 2012;107:588-91. doi:10.1038/bjc.2012.307
108 Pignata S, Lorusso D, Joly F, et al. Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line treatment: The randomized phase 3 trial MITO16B-MaNGO OV2B-ENGOT OV17. *J Clin Oncol* 2018;36(15_suppl):5506. doi:10.1200/JCO.2018.36.15_suppl.5506
109 Essel KG. PARPi after PARPi in epithelial ovarian cancer. Presented at: 2019 SGO Annual Meeting; March 16-19, 2019; Honolulu, HI. Abstract 7. https://www.onclive.com/view/repeat-use-of-parp-inhibitors-could-be-effective-strategy-in-ovarian-cancer.
110 Pujade-Lauraine E, Ledermann JA, Selle F, et al, SOLO2/ENGOT-Ov21 investigators. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017;18:1274-84. doi:10.1016/S1470-2045(17)30469-2
111 Coleman RL, Oza AM, Lorusso D, et al, ARIEL3 investigators. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;390:1949-61. doi:10.1016/S0140-6736(17)32440-6
112 Mirza MR, Monk BJ, Herrstedt J, et al, ENGOT-OV16/NOVA Investigators. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med* 2016;375:2154-64. doi:10.1056/NEJMoa1611310
113 Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. *Lancet Oncol* 2014;15:1207-14. doi:10.1016/S1470-2045(14)70391-2
114 AstraZeneca. Update on Phase III GY004 trial for cediranib added to Lynparza in platinum-sensitive relapsed ovarian cancer. 2020. https://bit.ly/2W8kpb0.
115 Markman M, Blessing J, Rubin SC, Connor J, Hanjani P, Waggoner S, Gynecologic Oncology Group. Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. *Gynecol Oncol* 2006;101:436-40. doi:10.1016/j.ygyno.2005.10.036
116 Gordon AN, Tonda M, Sun S, Rackoff W, Doxil Study 30-49 Investigators. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. *Gynecol Oncol* 2004;95:1-8. doi:10.1016/j.ygyno.2004.07.011
117 Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol* 2001;19:3312-22. doi:10.1200/JCO.2001.19.14.3312
118 Richardson DL, Backes FJ, Seamon LG, et al. Combination gemcitabine, platinum, and bevacizumab for the treatment of recurrent ovarian cancer. *Gynecol Oncol* 2008;111:461-6. doi:10.1016/j.ygyno.2008.08.011
119 Konstantinopoulos PA, Waggoner S, Vidal GA, et al. Single-Arm Phases 1 and 2 Trial of Niraparib in Combination With Pembrolizumab in Patients With Recurrent Platinum-Resistant Ovarian Carcinoma. *JAMA Oncol* 2019;5:1141-9. doi:10.1001/jamaoncol.2019.1048
120 Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol* 2019;20:636-48. doi:10.1016/S1470-2045(19)30029-4
121 Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al, KEYNOTE-189 Investigators. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med* 2018;378:2078-92. doi:10.1056/NEJMoa1801005
122 Rini BI, Plimack ER, Stus V, et al, KEYNOTE-426 Investigators. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med* 2019;380:1116-27. doi:10.1056/NEJMoa1816714
123 Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol* 2019;20:1239-51. doi:10.1016/S1470-2045(19)30388-2
124 Wang Z, Sun K, Xiao Y, et al. Niraparib activates interferon signaling and potentiates anti-PD-1 antibody efficacy in tumor models. *Sci Rep* 2019;9:1853. doi:10.1038/s41598-019-38534-6
125 Drew Y, Jonge M, Hong SH, et al. An open-label, phase II basket study of olaparib and durvalumab (MEDIOLA): Results in germline BRCA -mutated (gBRCA m) platinum-sensitive relapsed (PSR) ovarian cancer (OC). *Gynecol Oncol* 2018;149:246-7. doi:10.1016/j.ygyno.2018.04.555
126 Liu JF, Herold C, Gray KP, et al. Assessment of Combined Nivolumab and Bevacizumab in Relapsed Ovarian Cancer: A Phase 2 Clinical Trial. *JAMA Oncol* 2019;5:1731-8. doi:10.1001/jamaoncol.2019.3343

127 Hamanishi J, Mandai M, Ikeda T, et al. Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. *J Clin Oncol* 2015;33:4015-22. doi:10.1200/JCO.2015.62.3397
128 Zamarin D, Burger RA, Sill MW, et al. Randomized Phase II Trial of Nivolumab Versus Nivolumab and Ipilimumab for Recurrent or Persistent Ovarian Cancer: An NRG Oncology Study. *J Clin Oncol* 2020;38:1814-23. doi:10.1200/JCO.19.02059
129 O'Malley DM, Matulonis UA, Birrer MJ, et al. Phase Ib study of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer. *Gynecol Oncol* 2020;157:379-85. doi:10.1016/j.ygyno.2020.01.037
130 Caliman LP, Tavares RL, Piedade JB, et al. Evaluation of microsatellite instability in women with epithelial ovarian cancer. *Oncol Lett* 2012;4:556-60. doi:10.3892/ol.2012.776
131 Varga A, Piha-Paul S, Ott PA, et al. Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: Analysis of KEYNOTE-028. *Gynecol Oncol* 2019;152:243-50. doi:10.1016/j.ygyno.2018.11.017
132 Coon ME, Stephan SB, Gupta V, Kealey CP, Stephan MT. Nitinol thin films functionalized with CAR-T cells for the treatment of solid tumours. *Nat Biomed Eng* 2020;4:195-206. doi:10.1038/s41551-019-0486-0
133 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): NCCN Guidelines for Palliative Care. Version 1. 2020. https://www.nccn.org/professionals/physician_gls/pdf/palliative.pdf.
134 Gaertner J, Siemens W, Meerpohl JJ, et al. Effect of specialist palliative care services on quality of life in adults with advanced incurable illness in hospital, hospice, or community settings: systematic review and meta-analysis. *BMJ* 2017;357:j2925. doi:10.1136/bmj.j2925
135 Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733-42. doi:10.1056/NEJMoa1000678
136 Bakitas MA, Tosteson TD, Li Z, et al. Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. *J Clin Oncol* 2015;33:1438-45. doi:10.1200/JCO.2014.58.6362
137 National Comprehensive Cancer Network. Europe. https://www.nccn.org/global/europe.aspx.
138 Journal of Clinical Oncology. Advances in the Management of Gynecologic Cancers. 2019. https://ascopubs.org/jco/special-series/2019/gynecologic-cancer-management.
139 Lheureux S, Mirza M, Coleman R. The DNA repair pathway as a target for novel drugs in gynecologic cancers. *J Clin Oncol* 2019;37:2449-59. doi:10.1200/JCO.19.00347