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Epithelial Ovarian Cancer: Management of Advanced Disease

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INTRODUCTION

Epithelial ovarian cancer is the fifth leading cause of cancer death among women in the United States.[1] Most women with ovarian cancer present at an advanced stage (International Federation of Gynecology and Obstetrics stage III), for which the standard treatment remains cytoreductive surgery followed by platinum- and taxane-based combination chemotherapy. Although this treatment frequently is curative for patients with early-stage disease, more than 60% of women with advanced disease will develop recurrent disease with progressively shorter disease-free intervals.[2,3] However, there are many clinical trials in progress that are aimed at refining current therapy and evaluating different approaches to postoperative therapy, with the goal of improving prognosis and quality of life.

This manual, the second of a 2-part manual on epithelial ovarian cancer, discusses the management of advanced ovarian carcinoma. It defines treatment for advanced disease by describing the clinical trials which have resulted in the present treatment options, and also reviews the molecular targeted therapies which have application to present and future treatment. The first manual discussed evaluation, staging, and surgery for ovarian cancer as well as management of stage I and II disease; it was published in the *Hospital Physician Oncology Board Review Manual*, Volume 11, Part 2.[4]

CASE PATIENT

INITIAL PRESENTATION AND MANAGEMENT

A 47-year-old woman, G2P2, who works in a professional capacity presents with a several-month history of subtle indigestion-type symptoms as well as mild constipation, which persist. She has noticed increased abdominal girth and early satiety over several weeks, and these progressive symptoms caused her to schedule consultations with both gynecology and gastroenterology.

She is current on prevention studies, including mammography, and is knowledgeable about her significant family history, although she has not pursued genetic evaluation. Her family is of Russian descent and her mother was diagnosed with breast cancer at age 35 years and died from her

disease. A maternal aunt was diagnosed with ovarian cancer and died at age 55. A maternal grandfather had colon cancer diagnosed at age 82, and another maternal aunt was diagnosed with breast cancer 11 years ago while in her 50s and is without recurrence.

A pelvic ultrasound is performed while endoscopy is scheduled since her symptoms of abdominal bloating, early satiety, and change in bowel habits are possibly consistent with a gynecologic etiology. On the ultrasound evaluation, a complex cystic, solid mass extending from right to left adnexa measuring 8.6 × 5.0 × 9.3 cm is noted. A large amount of ascites is present. The patient is referred to a gynecologic surgeon, who recommends preoperative testing including computed tomography (CT) of the chest, abdomen, and pelvis and complete lab work with complete blood count with differential, comprehensive chemistry, and measurement of cancer antigen 125 (CA-125).

The staging CT demonstrates disease within the abdomen and pelvis but no evidence of chest involvement such as adenopathy, effusion, or pulmonary nodules. Within the abdomen and pelvis, ascites, peritoneal implants, omental cake, bilateral adnexal masses, and possible implants on the sigmoid colon are noted. The CA-125 is elevated at 1173 U/mL.

- **What is the primary treatment for advanced ovarian cancer?**

PRIMARY TREATMENT

Advanced disease is defined as stage III and IV disease. Both stages can result in surgery with optimal cytoreduction to no gross residual. Treatment options after surgery could include intraperitoneal (IP) chemotherapy, standard every 3-week chemotherapy with a taxane/platinum agent depending on the completed surgical result, and then treatment as outlined by the National Comprehensive Cancer Network (NCCN) guidelines.[5] A neoadjuvant regimen with taxane and platinum doublet is recommended when surgery is not an initial option. This treatment option is typically decided upon when there is large-volume of intraabdominal disease, disease involving a solid organ, or significant ascites or pleural effusion. Also, a dose-dense regimen with carboplatin and weekly paclitaxel is being tested in a clinical trial through the Japanese Gynecologic Oncology Group (JGOG).

Intraperitoneal/Intravenous Chemotherapy

The majority of patients with ovarian cancer will have advanced (stage III or IV) disease at the time of diagnosis. The standard treatment for optimally cytoreduced women is intravenous (IV)/IP therapy with paclitaxel and cisplatin as per the NCCN guidelines. Three U.S.-based phase 3 clinical trials[6–8] have been conducted to assess the efficacy of IP/IV therapy in women with optimally cytoreduced advanced ovarian cancer based on the theory that regional delivery of cytotoxic drugs directly into the peritoneal cavity will result in higher local concentrations of drug than can be safely reached with systemic IV chemotherapy alone.

Alberts and colleagues enrolled 654 patients with optimally cytoreduced (defined by the study as no residual disease exceeding 2 cm) stage III disease.[6] The study design randomly assigned patients to either an IV arm, consisting of IV cyclophosphamide 600 mg/m^2 and IV cisplatin 100 mg/m^2, or an IV/IP arm, consisting of IV cyclophosphamide 600 mg/m^2 and IP cisplatin 100 mg/m^2. An overall survival (OS) benefit was observed in the IV/IP arm, with a median survival of 49 months, as compared to 41 months in the IV arm ($P = 0.02$). However, the bene-

fit of IP cisplatin was questioned because paclitaxel was not given as part of either regimen.

Markman and colleagues randomly assigned 523 patients with optimally cytoreduced disease (defined as no residual disease >1 cm) to a regimen of IV cisplatin and paclitaxel or a regimen of IV carboplatin followed by IP cisplatin and IV paclitaxel.[7] A statistically significant longer progression-free survival (PFS) was associated with the use of IP therapy (27.9 months) as compared with IV therapy (22.2 months; $P = 0.01$). Although the OS for the IP arm was longer than the OS in the IV arm (63.2 vs 52.2 months), this difference did not achieve statistical significance. Furthermore, the IP regimen resulted in significant patient toxicities. Critics also argued that patients in the IP arm received an increased dose of chemotherapy due to the addition of IV carboplatin, and the overall benefit of IP chemotherapy in this setting was felt to be still unclear.[7]

In a phase 3 randomized trial (GOG 172),[8] 415 patients with optimally cytoreduced ovarian cancer (defined as no residual disease >1 cm) were randomly assigned to receive either IV paclitaxel (135 mg/mg infused over 24 hours) on day 1 followed by IV cisplatin (75 mg/m^2) on day 2, or IV paclitaxel (135 mg/m^2 infused over 24 hours) on day 1, IP cisplatin (100 mg/m^2) on day 2, and IP paclitaxel (60 mg/m^2) on day 8. For each regimen, treatment was given every 3 weeks for 6 cycles. The OS was 65.6 months in the IV/IP arm versus 49.7 months in the IV arm ($P = 0.03$). This survival benefit was observed despite only a 42% completion rate of all 6 cycles of IP-based chemotherapy, with most patients transitioning to IV platinum/taxane-based chemotherapy to complete the full 6 cycles.[8]

Based upon the GOG 172 study,[8] the National Cancer Institute recommended that women with optimally cytoreduced stage III ovarian cancer should be counseled about the clinical benefit associated with a combined regimen of IV and IP chemotherapy.[9] A meta-analysis of all trials comparing IP and IV chemotherapy demonstrated a survival benefit in favor of the IP regimens.[10] An updated review in 2011 compared standard chemotherapy with chemotherapy regimens that incorporated an IP component and noted an increase in OS and PFS in the groups incorporating IP chemotherapy.[11] Based upon currently available evidence and the survival benefit observed with IP chemotherapy, this therapy has now been incorporated into the NCCN guidelines for management of stage II–IV ovarian cancer based on patient characteristics.[5]

There are additional toxicities which have to be addressed when using IP chemotherapy, such as catheter-related infection, bowel perforation, the potential for peritonitis, and more quality of life issues, but progress has been made with more effective antiemetics and use of growth factor, which have improved patient quality of life.

A recent GOG analysis of the IP data from cooperative group clinical trials was conducted to evaluate the prognostic factors for stage III disease.[12] The analysis included 428 patients with stage III disease who were optimally cytoreduced (<1 cm) and received IP paclitaxel/platinum chemotherapy. The endpoints evaluated were PFS and OS. Results showed a PFS of 24.9 months and median OS of 61.8 months. The predictors for PFS were histology, surgical stage, and residual disease, whereas age, histology, and residual disease were prognostic for OS. Of these 428 patients, 36% had no residual disease; in the group with no residual disease, the PFS was 43.2 months and the median OS was 110 months. The conclusion was that age, histology, and extent of residual disease were predictors for OS and those patients with no residual

followed by IP treatment had improved OS compared with previously reported rates.[12]

Also, the results of a meta-analysis of GOG 114 and GOG 172 support the long-term survival advantage of IP chemotherapy.[13] The median follow-up time for the patients in these 2 studies was 10.7 years. The authors of the meta-analysis concluded that there was a significant difference in OS between the IP and IV treatment groups (61.8 months vs 51.4 months, $P = 0.048$). IP therapy was associated with a 23% reduction in the risk of death (adjusted hazard ratio [HR] 0.77; 95% CI 0.65 to 0.90; $P = 0.002$), and improved survival with gross residual disease of less than 1 cm. Factors associated with a poorer survival included clear cell/mucinous versus serous histology, gross residual versus no visible disease, and fewer cycles of IP therapy. Therefore, after this extended follow-up evaluation, the survival advantage of IP over IV continues to be demonstrated.[13]

Intravenous Chemotherapy: Historical Studies

The combination of taxane and platinum has been used to treat ovarian carcinoma since GOG 111 showed combination cisplatin and paclitaxel was superior to cisplatin and cyclophosphamide.[14] This landmark study by McGuire et al in 1996 established the superiority of combination platinum and paclitaxel for systemic treatment of advanced ovarian cancer. In this study, 410 patients with suboptimally debulked (residual disease >1 cm) stage III or IV disease were randomized to receive either IV cisplatin and cyclophosphamide or IV cisplatin and paclitaxel. Response rates were significantly better in the cisplatin/paclitaxel arm (73% vs 60%, $P = 0.01$), and OS was significantly longer in the cisplatin/paclitaxel arm as well (38 months vs 24 months, $P < 0.001$).

The second International Collaborative Ovarian Neoplasm (ICON 2) study was a large randomized trial designed to compare cyclophosphamide/doxorubicin/cisplatin (CAP) with single-agent carboplatin in women diagnosed with ovarian cancer.[15] This study entered 1526 women. Dosing for the CAP group was cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, and cisplatin 50 mg/m^2. Carboplatin was dosed to an area under the curve (AUC) of 5. The survival curves showed no survival benefit of CAP over carboplatin (HR 1.00, $P = 0.98$). Median survival was 33 months, and 2-year survival of 60% was noted for both groups, with CAP more toxic than single-agent carboplatin. The conclusion was that carboplatin was determined to be a safe and appropriate standard of treatment in this group.

Next, studies were designed to demonstrate that carboplatin and paclitaxel are equivalent to cisplatin and paclitaxel. This was shown in GOG 158, which compared carboplatin and paclitaxel with cisplatin and paclitaxel in optimally cytoreduced stage III ovarian cancer.[16] This noninferiority study randomly assigned 792 women with no residual mass greater than 1.0 cm post-surgery into 2 cohorts. Cohort 1 received cisplatin 75 mg/m^2 plus 24-hour infusion of paclitaxel at 135 mg/m^2 and cohort 2 received carboplatin AUC 7.5 plus paclitaxel 175 mg/m^2 over 3 hours. There was more toxicity in cohort 1, including grade 4 leukopenia, while grade 2 or greater thrombocytopenia was more common in cohort 2 and neurologic toxicity was similar in both cohorts. The median PFS was 19.4 months and OS was 48.7 months in cohort 1, while PFS was 20.7 months and OS was 48.7 months in cohort 2. Based on these results, paclitaxel and carboplatin were considered less toxic, easier to administer, and not inferior to cisplatin and paclitaxel and became the standard of care for treatment of advanced ovarian cancer.[16] A second randomized phase 3 study has confirmed these results.[17]

ICON 3 was the largest randomized trial to compare carboplatin plus paclitaxel with carboplatin alone or CAP (cyclophosphamide/doxorubicin/cisplatin), with the treatment option chosen per patient/physician prior to randomization.[18] This combination was chosen since the results from ICON 2, although immature at the time ICON 3 started, appeared to indicate that CAP and carboplatin were equivalent. In this study, 2074 women were randomly assigned to either paclitaxel and carboplatin (P/C), or CAP, or carboplatin. The primary outcome of this study was OS with secondary measures of PFS and toxicity. Patients received paclitaxel at a dose of 175 mg/m^2 (3-hour infusion) in combination with carboplatin dosed at AUC 5 or 6, with the control arm receiving either CAP or carboplatin. Patients were randomly assigned 2:1 in favor of the control arm. There was no difference in OS between the groups (HR 0.98, $P = 0.74$). The median OS was 36.1 months in the P/C group and 35.4 months in the control groups. The P/C group had more side effects, including alopecia, fever, and neuropathy, than carboplatin alone. The results were interpreted as showing single carboplatin and CAP to be as effective as the combination of paclitaxel and carboplatin for first-line treatment in ovarian cancer.

The results of the Scottish Randomized Trial in Ovarian Cancer (SCOTROC) suggest that an alternative regimen of docetaxel and carboplatin is similar to paclitaxel and carboplatin in terms of survival.[19] Combination docetaxel and carboplatin caused significantly more grade 3-4 myelosuppression (94% vs 84%; $P < 0.001$) but less grade 2 or higher neurotoxicity (11% vs 30%; $P < 0.001$) than combination paclitaxel and carboplatin.

Other Cytotoxic Agents

As new cytotoxic agents became available, the benefit of adding drugs to the carboplatin/paclitaxel regimen was considered. This concept was tested in GOG 182/ICON 5, an international 5-arm, randomized phase 3 trial that accrued 4312 women and was designed to determine whether an additional agent would improve OS and PFS in women with stage III-IV disease.[20] There were 5 treatment arms and each treatment regimen included 8 cycles given as a triplet or sequential-doublet. The design provided that there would be a minimum of 4 experimental cycles with at least 4 cycles of carboplatin and paclitaxel in each arm. The arms included: for the first 4 cycles, (1) paclitaxel 175 mg/m^2 and carboplatin AUC 6; (2) paclitaxel 175 mg/m^2 and gemcitabine 800 mg/m^2 days 1 and 8, and carboplatin AUC 5; (3) paclitaxel 175 mg/m^2 and pegylated liposomal doxorubicin (PLD) 30 mg/m^2 day 1, and carboplatin AUC 5; (4) paclitaxel 175 mg/m^2 and topotecan 1.25 mg/m^2 days 1, 2, 3, and carboplatin AUC 6; and (5) paclitaxel 175 mg/m^2 and gemcitabine 1000 mg/m^2 days 1 and 8, and carboplatin AUC 6. For cycles 5 to 8, all arms received paclitaxel 175 mg/m^2, with carboplatin AUC 6 given in arms 1, 4 and 5, while arms 2 and 3 received carboplatin AUC 5. Analysis failed to show a difference in PFS or OS within any of the experimental arms, and survival analysis defined by either optimal or suboptimal cytoreduction also showed no significant benefit in any subgroup. Therefore paclitaxel and carboplatin remained the standard of treatment.[20]

Two completed upfront trials have been published, GOG 218 and ICON 7. GOG 218 was a randomized, double-blinded, 3-armed placebo study for stage III and IV disease enrolling 1873 women with residual disease after primary cytoreductive surgery.[21] Arm 1 (control) was standard paclitaxel and carboplatin with placebo added in cycles 2 through 22; arm 2 added bevacizumab (15 mg/m^2) during the chemotherapy portion in cycles 2 through

6 and placebo in cycles 7 through 22 (bevacizumab-initiation); and arm 3 added bevacizumab both with chemotherapy (starting with cycle 2) and then continuing as maintenance for 15 months (bevacizumab-throughout). Grade 2 and greater hypertension occurred more frequently in the bevacizumab arms (bevacizumab-initiation 16.2%, bevacizumab-throughout 22.9%) compared with the control arm (7.2%). The primary end point was PFS, which was 10.3 months in the control arm, 11.1 months in the bevacizumab-initiation group, and 14.1 months in the bevacizumab-throughout group. Compared with the control arm, the HR for progression or death for the bevacizumab-throughout arm was 0.717 ($P < 0.001$). No benefit was noted when bevacizumab was given with chemotherapy only (bevacizumab-initiation, HR 0.908, $P = 0.16$). Also, there was no difference in OS noted among the 3 arms during this data analysis.[21]

ICON 7 was an open-label phase 3 trial of high-risk early-stage or advanced-stage ovarian cancer. There were 2 treatment arms: carboplatin AUC 5 or 6 and paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles, and this regimen plus bevacizumab at 7.5 mg/kg every 3 weeks for 5 or 6 cycles of chemotherapy and continued for 12 additional cycles.[22] Hypertension was noted in 18% of patients in the bevacizumab arm (2% in the control arm). The PFS at 36 months was better in the bevacizumab arm compared with the control arm (21.8 vs 20.3 months; HR 0.81, $P = 0.004$). The final update at 49 months was reported as a restricted mean survival time improvement of 0.9 months (44.6 vs 45.5 months for the bevacizumab and chemotherapy arm, $P = 0.85$). The high-risk group (stage III with >1 cm residual or stage IV) noted benefit in the bevacizumab arm compared with control (14.5 vs 18.1 months).[23]

In both of these studies, bevacizumab was well tolerated, hypertension was noted but not significant, and gastrointestinal perforation and proteinuria were uncommon. Also, there are differences between these 2 studies. In the ICON 7 trial, the bevacizumab dose was half that in the GOG 218 trial and the duration of use was shorter (12 vs 16 cycles). The maximum benefit of bevacizumab was seen at 12 months (at the time of bevacizumab completion) and not at 24 months, raising the question of how long to administer this agent. As a result of GOG 218 and ICON 7, bevacizumab was approved by the European Medicines Agency in December 2011 for use in ovarian cancer, knowing that cost will be a defining issue.[24] A summary of trials of bevacizumab is shown in **Table 1**.[21,22,25–28]

The Arbeitsgemeinschaft Gynäekologische Onkologie (AGO) has completed recruitment for a randomized phase 3 trial evaluating the optimal treatment duration of first-line bevacizumab in combination with standard paclitaxel and carboplatin (AGO/OVAR 17). The results are planned for 2017.

CASE CONTINUED

After preoperative clearance, treatment options are discussed with the patient prior to surgery. Given the possibility of optimal cytoreduction, the IP/IV chemotherapy protocol is reviewed with the patient since the IP port will be placed at the time of surgery if optimal cytoreduction is achieved. The procedure is performed with no gross residual noted and the IP portacath is placed. The patient recovers without complication.

At her postoperative visit, the IP/IV treatment program is discussed. For stage IIIC disease, IP therapy is recommended per the NCCN guidelines. Following her first cycle, the CA-125 level declines to 305 U/mL when tested on day 1 of cycle 2. On day 1 of cycle 3, the marker is 49 U/mL.

Table 1. Trials of Bevacizumab in Treatment of Ovarian Cancer

Trial	Stage	Regimen	Outcome	Toxicity
GOG170D[25]	Recurrent	BV	CR 21% SD 52% OS 17 mo PFS 4.7 mo	Grade 3 HTN 10% Grade 3/4 GI events 7%
NCI 5789[26]	Recurrent	BV 10 mg/kg plus oral cyclophosphamide 50 mg daily	PR 24% SD 63% OS 16.9 mo	Grade 3 HTN 16% Grade 3 heme 23% GIP 4%
GOG 218[21]	Primary	Carboplatin + paclitaxel followed by arm 1–no BV, Arm 2–BV with CT for cycles 2-6, Arm 3–BV throughout CT and as maintenance	PFS: Arm 1 10.3 mo Arm 2 11.1 mo Arm 3 14.1 mo OS: no difference among 3 arms	Grade 2 HTN: Arm 1 7.2% Arm 2 16.2% Arm 3 22.9%
ICON-7[22]	Primary	Carboplatin + paclitaxel + BV 7.5 mg/Kg (or none), followed by BV 7.5 mg/kg (or none); 2 arms	PFS (at 42 mo): Arm 1 (no BV): 17.3 mo Arm 2 (BV): 19.8 mo	Grade 2 HTN: Arm 1 2.1% Arm 2 18.3% GIP 1.3% (arm 2)
AURELIA[27]	Recurrent PT-resistant	Paclitaxel or PLD or topotecan alone or with BV Cross over to BV after progression in CT arms	PFS: BV + CT 6.7 mo CT 3.4 mo OS: not significant	Grade 2 HTN and proteinuria in BV arms GIP 2.2% in BV arms
OCEANS[28]	Recurrent PT-sensitive	Carboplatin + gemcitabine + placebo (placebo arm) versus Carboplatin + gemcitabine + BV until progression (BV arm)	Median PFS: Placebo 8.4 mo BV 12.4 mo HR 0.46 (P <0.0001) OS: not significant	BV: HTN grade ≥3 17.4 % Proteinuria 8.5% TE events 6.8% Bleeding 6.5% GI events 2.4%

BV = bevacizumab; CR = clinical response; CT = chemotherapy; GIP = gastrointestinal perforation; HTN = hypertension; OS = overall survival; PFS = progression free survival; PLD = pegylated liposomal doxycycline; PR = partial response; PT= platinum; SD = stable disease; TE = thromboembolic.

Adapted from Bell-McGuinn K, Konner J, Tew W, Spriggs DR. New drugs for ovarian cancer. Ann Oncol 2011;Suppl8:viii77–viii82; *and* Monk BJ, Pujade-Lauraine, Burger RA. Integrating bevacizumab into the management of epithelial ovarian cancer: the controversy of front-line versus recurrent disease. Ann Oncol 2013;24 (suppl 10):x53–x58.

- **What is the role for dose-dense chemotherapy?**

Dose-Dense Chemotherapy

The concept of dose-dense chemotherapy (ddCT) is derived from mathematical models of tumor growth, specifically the Norton-Simon model. This model suggests that increasing the rate of chemotherapy delivery (or dose density of chemotherapy) and thereby shortening the interval between doses of cytotoxic chemotherapy agents effectively reduces the time for tumor regrowth between cycles.[29] This concept was initially demonstrated in breast cancer by the Cancer and Leukemia Group B (CALGB) C9344 study, and a meta-analysis of dose-dense chemotherapy in nonmetastatic breast cancer demonstrated better overall and disease-free survival.[30]

This concept was studied in patients with stage II-IV disease in the phase 3 JGOG 3016 trial.[31] In this trial, patients were randomly assigned to receive 6 cycles of either a conventional regimen of carboplatin AUC 6 and paclitaxel 180 mg/m^2 given on day 1 of a 3-week cycle, or a dose-dense regimen of carboplatin AUC 6 given on day 1 of a 3-week cycle and weekly paclitaxel at 80 mg/m^2. The initial evaluation at 29 months noted a PFS of 17.2 months in the standard arm and 28 months in the dose-dense arm (HR 0.71, 95% CI 0.58 to 0.88; P = 0.0015). The 3-year OS (42-month follow-up) favored the dose-dense group, with a PFS of 65.1 versus 72.1 months (HR 0.75, 95% CI 0.57 to 0.98; P = 0.03). The benefit seen in OS at 2 years was better in the ddCT arm compared with the standard regimen (83.6% vs 77.7%, P = 0.049). At 42 months, the OS in the ddCT arm was 72.1% and in the standard arm, 65.1% (P = 0.03). Early withdrawal due to toxicity was higher in the ddCT arm, and the most common adverse event in both arms was neutropenia. Grade 3/4 anemia occurred more frequently in the ddCT arm, but otherwise toxic effects were similar between the 2 arms.[31]

The results from this original study were recently updated.[32] In the ddCT group, PFS and OS were improved compared with the standard treatment regimen: median OS was 100.5 months in the ddCT group compared with 62.2 months in the standard treatment group, and 5-year overall OS was 58.7% in the ddCT arm compared with 51.1% in the standard group. Subgroup analysis noted the PFS and OS in clear-cell and mucinous tumors did not differ between arms. Also, the most significant benefit was noted in the group of patients with residual disease (1 cm or more) who presented with serous or nonclear-cell or mucinous histology. It should also be noted the study group comprised mostly Asian women, and there is evidence of ethnic differences in chemotherapy drug metabolism among these groups.[33]

Another recent study incorporating a variation on the ddCT concept is the Multicentre Italian Trials in Ovarian Cancer (MITO) 7.[34] This phase 3 trial randomly assigned women with ovarian cancer, fallopian tube cancer, and primary peritoneal cancer, stages IC–IV to either standard carboplatin AUC 6 and paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles or weekly carboplatin AUC 2 plus paclitaxel 60 mg/m^2 for 18 weeks. The median PFS was 17.3 months in the standard group and 18.3 months in the weekly schedule (HR 0.96, P = 0.66). Scores on the Functional Assessment of Cancer Therapy Ovarian Trial Outcome Index (FACT-O/TOI) differed between the 2 regimens, with worsening with every standard cycle but worsening in the first cycle of the weekly group and then remaining stable for the remainder of treatment. Grade 3/4 neutropenia occurred less frequently in the weekly group, as did thrombocytopenia and neuropathy.

ICON 8 accrued approximately 1500 women with ovarian cancer, fallopian tube cancer, and primary peritoneal cancer stages IC–IV, excluding those with low-risk stage I disease. This complex study randomly assigned women into 2 groups: either immediate primary surgery or delayed primary surgery and then treatment on 1 of 3 arms for each group: (1) paclitaxel 175 mg/m^2 and carboplatin AUC 5, (2) paclitaxel 80 mg/m^2 weekly and carboplatin AUC 5, or (3) weekly paclitaxel 80 mg/m^2 and carboplatin AUC 2. The next randomization is with the delayed surgery group whose initial chemotherapy is given as neoadjuvant, followed by surgery and then completion of 3 cycles of chemotherapy in the same arm of treatment as initially started. An update given at ASCO 2013 reported no significant change in PFS between the 2 arms (17.3 vs 18.3 months, HR 0.96), but quality of life was reported as improved in the

weekly group. This study closed November 2014, with results in review.

GOG 262 is another study evaluating the ddCT approach in women with ovarian cancer, fallopian tube cancer, and primary peritoneal cancer but who have suboptimal cytoreduction, stage II–IV disease.[35] Bevacizumab is incorporated in both treatment arms as well as maintenance and is considered optional treatment in each. A conventional regimen of carboplatin AUC 6 with paclitaxel 175 mg/m^2 plus bevacizumab at 15 mg/m^2 starting at cycle 2 was compared to a ddCT regimen of carboplatin AUC 6 and paclitaxel 80 mg/m^2 weekly, again with bevacizumab starting with cycle 2. Each cycle is 3 weeks and the course for each arm is 6 cycles. The study closed in 2012, with results noting no significant difference in PFS between the ddCT group and standard treatment group (HR 0.97, 95% CI 0.79 to 1.18). Also, in the group of women who did not receive bevacizumab, the ddCT group did better in terms of PFS than the standard group (14 vs 10 months, HR 0.60, 95% CI 0.37 to 0.96). In women receiving bevacizumab, the PFS was similar in both groups (15 months with HR of 1.06). The results of this study raise the question of whether the benefit from the ddCT can be separated from the maintenance bevacizumab. The study closed in February 2012 and preliminary results were presented at ASCO 2013.

Aside from the surgical debate for management of advanced patients, trials such as GOG 262, MITO 7, and ICON 8 will hopefully provide information regarding the roles of both neoadjuvant and ddCT in the management of woman with advanced disease. A summary of ddCT trials is provided in **Table 2**.

- **What is the role for neoadjuvant chemotherapy?**

NEOADJUVANT CHEMOTHERAPY

For patients who are suboptimally cytoreduced (residual cancer >1 cm), IV chemotherapy with carboplatin and paclitaxel remains the treatment of choice. However, in those patients who are unable to undergo primary optimal cytoreductive surgery or who have unresectable disease, consideration can be given for palliative neoadjuvant platinum-based therapy.

Recently, the European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC) conducted a randomized study in advanced disease, specifically stage IIIC and IV. This study randomly assigned 670 women (out of 718 who were enrolled) to either standard treatment with primary cytoreductive surgery followed by at least 6 cycles of platinum-based chemotherapy or to 3 cycles of neoadjuvant platinum-based chemotherapy followed by interval cytoreductive surgery and then at least 3 cycles of platinum-based chemotherapy.[36] The results showed that among this group of women, survival was similar between the groups: 29 months in the surgery group versus 30 months in the neoadjuvant group, with a median PFS in both groups of 12 months. This study was further discussed at the 9th International Conference on Ovarian Cancer in relation to the ongoing debate regarding which women are appropriate for a neoadjuvant approach in advanced disease.[37] The concept that primary cytoreductive surgery should remain the standard of care for the majority of women presenting with advanced disease is discussed in detail by the authors in a recent commentary.[38]

At the ASCO 2014 meeting, a follow-up to the JCOG 0602 study was presented. This randomized, phase 3 study is evaluating primary surgery versus neoadjuvant chemotherapy (NAC) followed by interval cytoreductive surgery in women with

Table 2. Phase 3 Trials of Dose-Dense Chemotherapy for Treatment of Ovarian Cancer

Study	Eligibility	End Points	Design	Cycles	Results
JGOG 3016[31,32]	O, F, PP Residual disease allowed Stage II–IV No prior therapy Accrual: 637 participants, closed 12/2005	Primary: PFS Secondary: OS	Cohort 1: Paclitaxel 180 mg/m^2 Carboplatin AUC 6 Cohort 2: Paclitaxel 80 mg/m^2/week × 3 Carboplatin AUC 6	6–9 6–9	PFS HR = 0.71 (P = 0.71) 3-yr OS favored ddCT group (PFS = 65.1 vs 72.1 mo; HR = 0.75, P = 0.03) 2014 update: ddCT group showed improved OS (100.5 vs 62.2 mo) and 5-year OS (58.7% vs 51.5%) Significant benefit noted in patients with residual disease or serous or mucinous histology
GOG 262[35]	O, F, PP Suboptimal/NACT Stage III or IV Accrual: 1100 participants, closed 2/2012	Primary: PFS Secondary: OS	Cohort 1: Paclitaxel 175 mg/m^2 Carboplatin AUC 6 Bevacizumab 15 mg/kg can be added at cycles 2–6 Cohort 2: Paclitaxel 80 mg/m^2 (D1, 8, 15) Carboplatin AUC 6 (D1) Bevacizumab 15 mg/kg can be added at cycles 2–6	 ×6 ×6 ×6 ×6	No significant difference in PFS between cohorts (HR 0.97); however, without bevacizumab, ddCT group had a better PFS (14 vs 10 mo); with bevacizumab PFS was similar (15 mo for both cohorts, HR 1.06)
ICON 8	O, F, PP IC–IV IPS vs DPS Accrual: 1500 participants, estimated completion 6/2017	Primary: PFS Secondary: OS	Cohort 1: IPS Carboplatin AUC 5 Paclitaxel 175 mg/m^2 Cohort 2: IPS Carboplatin AUC 5 Paclitaxel 80 mg/m^2 (D1, 8, 15) Cohort 3: IPS Carboplatin AUC 2 (D1, 8, 15) Paclitaxel 80 mg/m^2 (D1, 8, 15) Cohort 1: DPS Carboplatin AUC 5 Paclitaxel 175 mg/m^2 Cohort 2: DPS Carboplatin AUC 5 Paclitaxel 80 mg/m^2 (D1, 8, 15) Cohort 3: DPS Carboplatin AUC 2 (D1, 8, 15) Paclitaxel 80 mg/m^2 (D1, 8, 15)	×6 ×6 ×6 ×3/DPS/×3 ×3/DPS/×3 ×3/DPS/×3	In review
MITO 7[34]	O, F, PP Residual disease allowed Stage IC–IV No prior therapy Accrual: 882 participants	Primary: QOL, PFS Secondary: OS	Cohort 1: Paclitaxel 60 mg/m^2 (D1, 8, 15) Carboplatin AUC 2 (D1, 8, 15) Cohort 2: Paclitaxel 175 mg/m^2 (D1) Carboplatin AUC 6 (D1)	 ×6 ×6 ×6 ×6	22-month follow-up presented at ASCO 2013 No change in PFS: 17.3 vs 18.3 mo (weekly); HR = 0.96 QOL improved for weekly cohort

ddCT = dose-dense chemotherapy; DPS = delayed primary surgery; F = fallopian tube; HR = hazard ratio; IPS = immediate primary surgery; O = epithelial ovarian; OS = overall survival; PFS = progression-free survival; PP = primary peritoneal; QOL = quality of life.

stage III and IV ovarian, tubal, and peritoneal cancers.[39] A total of 301 women have been accrued to either standard therapy (surgery followed by 8 cycles of doublet chemotherapy) or 4 cycles of NAC followed by interval cytoreduction and then completion of another 4 cycles of chemotherapy. The study is designed to determine noninferiority of survival within the neoadjuvant group. Interim results reported that the frequency of bowel or organ resection was lower in the NAC arm ($P < 0.01$) and the rate of overall adverse events was lower in the interval cytoreduction group; the primary analysis for OS is planned for 2016.[40] If confirmed, the NAC approach will be closer to validation, but there still needs to be data evaluating the standard end points of PFS and OS.

CASE CONTINUED

At the completion of treatment, remission is noted by normalization of CA-125 and no evidence of disease on staging CT. The patient has now completed the standard treatment course.

- **Is there a role for maintenance chemotherapy?**

MAINTENANCE CHEMOTHERAPY

The idea of consolidative therapy has been considered since the majority of women will achieve a complete or partial clinical response following some combination of surgery and platinum/taxane chemotherapy, and about half of that group will relapse within 18 to 24 months and at that point are deemed incurable. The finding that most women will respond to first-line treatment and then have a subsequent recurrence had led investigators to study prolonged treatment regimens. Unfortunately, none of these historical studies showed an OS benefit in the adjuvant setting.[41–43] IP therapy has also been studied as consolidation, but without benefit in OS.[44,45]

Maintenance chemotherapy has been studied as a way to possibly delay disease recurrence and prolong OS in patients who achieve remission following primary treatment. In a phase 3 trial (SWOG 9701/GOG 178), 277 patients with advanced ovarian cancer who had achieved clinical remission following first-line chemotherapy were randomly assigned to receive either 3 or 12 cycles of single-agent IV paclitaxel administered every 28 days as maintenance therapy.[41] Results demonstrated a shorter PFS in patients receiving 3 cycles of single-agent paclitaxel (21 months) as compared with patients receiving 12 cycles (28 mo, $P = 0.0035$). Other than peripheral neuropathy, there were no major toxicity differences noted between the regimens. However, the trial was stopped early due to this PFS advantage in the 12-cycle group, but OS was not able to be assessed. Therefore, without firm data to justify toxicity, this study did not constitute a maintenance standard.

GOG 212, the follow-up study to SWOG 9701/GOG 178, began accruing patients in 2005 but is now closed to accrual.[46] Patients with stage III or IV disease who are in a clinical remission after adjuvant therapy are then randomized into 1 of the following treatment arms: (1) observation, (2) paclitaxel once monthly for 12 months, or (3) experimental arm, paclitaxel poliglumex, a novel formulation of paclitaxel, given once monthly for 12 months. The primary outcome is OS. Patients who complete study treatment then have scheduled follow-up for 10 years. The final data collection date for primary outcome measure is January 2022. The results of this study will help define the benefits, if any, of maintenance chemotherapy.

CASE CONCLUSION

The patient continues with surveillance visits conducted every 3 months. This includes alternating follow-up visits with gynecologic surgery and medi-

cal oncology, lab work including CA-125, and physical evaluation including pelvic exam every other visit. At the completion of 2 years, her follow up visits will change to every 6 months through a total of 5 years.

- **How would one manage recurrent disease?**

MANAGEMENT OF RECURRENT DISEASE

Timing of Therapy

The optimal timing to initiate salvage therapy for recurrent ovarian cancer remains somewhat unclear. Closely monitoring CA-125 levels is part of routine surveillance in the United States. Therefore, disease recurrence is often diagnosed at a time when the patient is still asymptomatic. In many cases of recurrence, chemotherapy is palliative, and some experts have proposed that treatment can be deferred until the patient becomes symptomatic from her cancer. An alternative perspective argues that small volume disease may respond better to early intervention, and that treatment should be initiated at the time of recurrence regardless of the bulk of cancer. Two trials, GOG 198 and Medical Research Council (MRC) OV05/EORTC 55955, evaluated whether there was increased benefit with initiating treatment at the time of asymptomatic recurrence. The phase II GOG 198 trial randomly assigned patients to either tamoxifen or thalidomide at the time of biochemical recurrence, as determined by CA-125 levels, with PFS as the end point.[47] This study was closed due to lack of benefit.

In Europe, the MRC and EORTC together conducted a trial (OV05/55955) to evaluate the benefit of early intervention based on marker elevation in an asymptomatic woman versus beginning treatment when symptomatic.[48] This study randomly assigned 1442 women who were in complete remission after first-line platinum-based chemotherapy and achieved a normal CA-125 into 2 groups after the CA-125 had exceeded twice the upper limit of normal. The groups received either early or delayed chemotherapy, with all patients treated according to the standard local practice. Women assigned to the delayed group received treatment once symptoms developed. The results showed no evidence of a difference in the OS between early and delayed treatment (HR 0.98, $P = 0.85$). Median survival for the early group was 25.7 months compared with 27.1 months for those on the delayed treatment. Therefore, no survival benefit was noted with early treatment based on the rising CA-125 alone, and the value of routine measurement of this marker in follow-up management of patients who have attained a complete response after first-line treatment was not proven.[48] However, in the case of a rising CA-125 in an asymptomatic woman who has achieved a prolonged disease-free interval (at least 12-month DFI), this concept would not be applicable and a workup should be considered.

Secondary Surgical Cytoreduction and Palliative Surgery

There is ongoing debate over the role of secondary cytoreduction in the setting of recurrent disease given that cure is typically not an option in this group of patients. However, there is a defined survival benefit if a patient does achieve optimal secondary cytoreduction in the setting of a prior prolonged DFI and limited distribution of recurrent disease.[49] There are clinical trials presently accruing patients to specifically address the question of OS in the setting of secondary cytoreduction for limited recurrent disease. Studies presently enrolling patients include DESKTOP 3, managed by the AGO, which is accruing patients with platinum-sensitive disease

and assigning them to either second cytoreduction or no surgery,[50] GOG 213,[51] and SOCceR.[52]

Also, the pre-enrollment data from the CALYPSO trial was evaluated since a percentage of patients had secondary cytoreductive surgery performed at the discretion of the gynecologic surgeon prior to enrolling.[53] The analysis found a median OS of 49.9 months in the group receiving surgery prior to beginning chemotherapy and 29.7 months for those patients who received chemotherapy alone (HR 0.68, $P < 0.004$). Additionally, there was a 57% reduction in risk of death in the surgery first group, and the probability of survival at 3 years was 88% for that group compared with 66% for the chemotherapy-alone group. Given these findings, further evaluation is needed to determine the role of surgery in patients with recurrent platinum-sensitive disease.

Palliative surgery is used to manage bowel obstruction in women with recurrent disease, which typically affects the small bowel. Studies have tried to define those women who will have a better outcome from a surgical procedure,[54] but to date a clinical trial has not been completed to specifically define this population.

Predictors of Outcome

The treatment-free interval (TFI) following completion of initial therapy is one of the most important predictors of outcome and response to further treatment. A retrospective analysis of 72 patients initially treated with a platinum-based regimen demonstrated that response rates to repeat platinum-based therapy were dependent on the TFI, with response rates of 27% at a TFI of 5 to 12 months, 33% at 13 to 24 months, and 59% at greater than 24 months.[55] Patients who had a TFI of greater than 24 months and had not received additional treatments had a 77% response rate and a 32% surgical complete response rate. Given the importance of the TFI in predicting response, the GOG stratifies patients with recurrent disease into 1 of 3 categories: (1) *platinum-resistant disease*, defined as a TFI of less than 6 months following platinum-based therapy; (2) *platinum-refractory disease*, defined as progression of cancer during platinum-based therapy; and (3) *platinum-sensitive disease*, defined as a TFI of greater than 6 months after a platinum-based regimen. It is important to note that the TFI typically shortens with each subsequent treatment with platinum,[56] eventually evolving into platinum-resistant disease with decreasing overall response rates to chemotherapy, even in patients with initially platinum-sensitive disease at recurrence.

- **What are treatment options for recurrent platinum-sensitive disease?**

Platinum-Sensitive Disease

Single-agent therapy. The US Food and Drug Administration (FDA) has approved the use of cisplatin and carboplatin as single-agent treatments of recurrent ovarian cancer. The response rate to these agents as single therapy in platinum-sensitive disease is up to 50%,[57] and the degree of response rate depends on the length of the platinum-free interval (PFI) and whether the patient is primarily platinum-sensitive.[58] Cisplatin and carboplatin appear to have equivalent response rates in the recurrent setting, but their toxicity profiles differ.

Non-platinum single agents have also been studied in the setting of platinum-sensitive disease. Single-agent paclitaxel, topotecan, and PLD have all demonstrated efficacy in the setting of recurrent platinum-sensitive disease, with response rates between 20% and 30% in phase 3 trials.[59–61]

Combination therapy. Several key trials have been conducted to address whether platinum-based combination therapy is superior to single-agent therapy in recurrent platinum-sensitive disease. The results of 2 phase 3 trials were pooled and reported together as ICON 4/AGO.[62] In this combined study of these 2 parallel-run trials, 802 patients with platinum-sensitive recurrent ovarian cancer were enrolled between 1996 and 2002. Eligible patients were required to previously have received a platinum-based regimen at the time of initial diagnosis. The 2 trials differed in terms of the TFI: the TFI needed to be greater than 12 months for patients to be considered eligible in the ICON 4 trial and greater than 6 months in the AGO trial. In the ICON 4 trial, patients were randomized to receive either single-agent platinum or platinum with paclitaxel. There was an improved response rate (RR, 66% vs 54%, $P = 0.06$) and improved PFS (50% progression-free at 1 year vs 40%, $P < 0.001$) with the paclitaxel with platinum regimen; the group receiving this regimen also had an improved OS (57% alive at 2 years vs 50%, $P = 0.023$). In the AGO OVAR 2.5 study, patients considered platinum-sensitive were stratified to carboplatin or carboplatin/gemcitabine. The study demonstrated an improved RR (47% vs 31%, $P = 0.0016$) and PFS (8.6 vs 5.8 months, $P = 0.0038$) but no improvement in survival (18 vs 17.3 months, $P = 0.7349$). The study was insufficient to justify approval of the combination.[63]

Next GEICO (Grupo Espanol de Investigacion en Cancer de Ovari) conducted a phase 2 trial that randomly assigned 81 patients to treatment with carboplatin or carboplatin plus paclitaxel and yielded similar results, with a response rate of 75.6% in the carboplatin/paclitaxel arm versus 50% in the carboplatin alone arm.[64] In another randomized phase 3 trial, GCIG (Gynecologic Cancer Intergroup) compared combination gemcitabine and carboplatin therapy with carboplatin alone in platinum-sensitive recurrent disease. Interim analysis of the data revealed an increased RR with the combination of gemcitabine/carboplatin therapy (47.2% vs 30.9%, $P = 0.0016$).[65] The HR for median OS was 0.96, and the HR for PFS was 0.72, with a median PFS of 8.6 months in the combined therapy arm versus 5.8 months in the carboplatin alone arm. Based upon these findings, the FDA approved gemcitabine in combination with carboplatin for use in women with advanced ovarian cancer who relapse at least 6 months after completion of previous platinum-based treatment.

Issues have been raised regarding the results from the ICON 4/AGO, GEICO, and GCIG trials. For example, a relatively low number (40%) of patients in ICON 4 had received a taxane during their initial therapy. However, 87.2% of the patients received a taxane as part of their initial therapy in the GEICO trial.[64] In addition, these trials do not address the possible role of sequential therapy in comparison with combined therapy. Combination regimens do result in higher response rates and will likely benefit the symptomatic patient more rapidly, but they also carry a higher rate of toxicity. In the ICON 4/AGO and GEICO trials, approximately 20% of the combined platinum and paclitaxel group experienced grade 2 to 4 neurological toxicity, and in the GCIG study, there was a 78.3% incidence of grade 3 or 4 hematologic toxicity with the combined carboplatin and gemcitabine regimen.[65]

The GCIG CALYPSO trial is the largest randomized clinical trial evaluating platinum-sensitive ovarian cancer. A total of 976 women were enrolled into this phase 3 study of PLD (30 mg/m^2) plus carboplatin (AUC 5) every 4 weeks versus carboplatin (AUC 5) and paclitaxel given every 4 weeks. The primary endpoint was the noninferiority

of PLD/carboplatin relative to carboplatin and paclitaxel in PFS. Women receiving PLD/carboplatin had a statistically significant improvement in PFS compared with women receiving carboplatin/paclitaxel (HR 0.82, $P = 0.005$). In addition, severe nonhematologic toxicity occurred less frequently in the PLD/carboplatin group (28.4% vs 36.8%, $P = 0.001$).[66] The final OS results from this study looked at whether the observed improvement in PFS translates into an OS for patients receiving the PLD/carboplatin regimen. The subgroup analysis included age, BMI, TFI, measurable disease, number of prior therapy lines, and ECOG performance status. There was no statistically significant difference between treatment arms in any of the subgroups. Therefore, the combination of PLD and carboplatin offers an option to the standard regimen of carboplatin and paclitaxel for platinum-sensitive disease.[67]

The OCEANS study was a randomized double-blind placebo phase 3 trial that evaluated the efficacy and safety of bevacizumab with gemcitabine and carboplatin for treating platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer and as maintenance for those women showing response to treatment.[28] Participants were randomly assigned to receive gemcitabine and carboplatin plus either bevacizumab or placebo for 6 to 10 cycles, with bevacizumab or placebo continued until disease progression. The group receiving bevacizumab had a superior median PFS (12.4 months) compared with the group receiving chemotherapy alone (8.4 months; HR 0.484). The objective response rate was improved with bevacizumab, 78.5% versus 57.4% ($P < 0.0001$). There were no new safety concerns, hypertension and proteinuria rates were higher in the bevacizumab group, and 2 patients in the bevacizumab group developed bowel perforation. The overall conclusion was that chemotherapy and bevacizumab followed by bevacizumab (maintenance) given until progression showed statistical significance in PFS compared with the chemotherapy arm alone.[28]

An ongoing phase 3 study (European Network of Gynaecological Oncological Trial Groups ov 17/MITO 16) in platinum-sensitive disease is evaluating second-line chemotherapy with and without bevacizumab after women have received chemotherapy with bevacizumab as first-line treatment. This trial opened in April 2013 and is presently accruing.

In summary, the studies to date in platinum-sensitive disease have demonstrated benefit with with a platinum doublet therapy. Furthermore, there is now data showing extended PFS with the addition of bevacizumab.

- **What are the treatment options for platinum-resistant disease?**

Platinum-Resistant Disease

Platinum-resistant cancer is defined as relapse within 6 months or less from treatment, whereas platinum-refractory disease is defined as disease progression while on a platinum regimen. Both carry a poor prognosis and management issues are control of symptoms and palliation. Due to this prognosis, the standard for treatment is single-agent chemotherapy. Additional treatment options may be available through clinical trial participation if the patient's performance status is appropriate. Therefore, the choice of therapy in this situation should be based upon ease of route of administration and avoidance of toxicities. There are multiple single chemotherapy drugs which have activity in this category (**Table 3**).[61,68–74]

The AURELIA trial was an international randomized trial which enrolled 361 women, 179 in the

Table 3. Chemotherapy Drugs for Platinum-Resistant Ovarian Cancer

Agent	ORR (%)	Median PFS (mo)	Median OS (mo)
PLD[61]	16	2.3	9
Topotecan[61]	8	3.4	10.3
Gemcitabine[68]	23	10.6	6.7
Vinorelbine[69]	21	3.1	10.1
Etoposide[70]	26.8	5.7	10.8
Irinotecan[71]	17.2	2.8	10.1
Pemetrexed[72]	21	2.9	11.4
Docetaxel[73]	35	5	8
Ifosfamide[74]	12	NR	9

ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

Adapted from Dizon DS, Campos SM. Dx/Rx: gynecologic cancer. Sudbury (MA): Jones and Bartlett Publishing; 2011.

bevacizumab plus chemotherapy arm and 182 in the chemotherapy alone arm.[27] Paclitaxel, PLD, and topotecan were the chemotherapy options. Treatment was continued until disease progression, unacceptable toxicity, and/or consent withdrawal occurred. The PFS was the primary end point and assessment demonstrated a statistically significant improvement in women who received bevacizumab plus chemotherapy (6.7 months) compared to those who received chemotherapy alone (3.4 months, HR 0.48, $P < 0.0001$). There was no significant difference in OS (16.6 vs 13.3 months). Also, the addition of bevacizumab to paclitaxel provided the largest improvement, resulting in a 5.7-month improvement in median PFS (9.6 months vs 3.9 months; HR 0.47), an improvement in the overall response rate (53% vs 30%), and a 9.2-month improvement in median OS (22.4 months vs 13.2 months; HR 0.64).[75] In November 2014, the FDA gave approval for the use of bevacizumab with single-agent chemotherapy for treatment of patients with platinum-resistant disease.

- **What is the next direction for finding better treatments in ovarian carcinoma?**

MOLECULAR TARGETED THERAPY

PARP Inhibitors

Poly (ADP-ribose) polymerase (PARP) is a family of nuclear proteins with enzymatic activity and ability to facilitate DNA repair, with PARP1 being the most tested within the group. It functions in the base excision repair system that repairs DNA damage induced by radiation and alkylating agents. The role of PARP1 in DNA repair has been extensively studied.[66] PARP-inhibitors, which inhibit the proteins PARP1 and PARP2, were initially described as demonstrating synthetic lethality in the setting of *BRCA* dysfunction.[76,77] This is the phenomenon where individual disruption of 2 independent genes does not cause cell death but the combined disruption is cytotoxic. Researchers showed that PARP1 inhibitors had cytotoxic effects on *BRCA1*- or *BRCA2*-deficient cells, which were caused by the lack of repair of single-strand DNA breaks (SSB) resulting from PARP1 inhibition and the lack of double-strand break (DSB) repair because of homologous recombination dysfunction due to *BRCA* mutation.[78] The homologous recombination system also attempts to correct DSB.[79]

The concept of "*BRCA*ness" has been defined as the phenotype that some sporadic tumors share with *BRCA* cancers, and patients with this phenotype can exhibit improved response and survival as seen in those women with true *BRCA* mutations. The underlying cause for *BRCA*ness is related to dysfunction within the homologous recombination system and mutations within the *BRCA1/BRCA2* genes. The frequency of this phenotype is estimated to be approximately 50% in the high-grade serous population. Several reviews offer expanded reading on this topic.[78,80]

Initial clinical studies demonstrated that PARP-inhibitors have single-agent activity in women with *BRCA*-related ovarian cancer who are platinum-sensitive as well as in women with *BRCA*-wild type ovarian cancer.[81–83] The phase 1 study of olaparib was done in combination with PLD in patients with advanced solid tumors.[84] This was an open-label, dose-finding study to evaluate safety and tolerability with study drug given either weekly or continuously for 28-day cycles. The study group tested consisted of 44 participants, with 28 ovarian, 13 breast, and 3 other cancers. The overall response rate (ORR) was 33%, with 7% complete remission and 26% partial remission. Thirteen responders were in the ovarian group; the ORR in the ovarian cancer subgroup was 50% (13 women), and 71% were platinum sensitive. Also, 61% had *BRCA* mutations. The results of this study were sufficient to continue with phase 2 testing.[84]

A randomized phase 2 trial compared the PARP-inhibitor olaparib to PLD in women with recurrent *BRCA*-related ovarian cancer which recurred within 12 months of platinum-based therapy.[85] The groups were assigned in a 1:1: ratio to either olaparib given at 200 mg or 400 mg twice per day or PLD 50 mg/m^2 every 28 days. The primary end point was PFS assessed by RECIST criteria. Secondary endpoints were ORR and safety. The median PFS was 6.5 months, 8.8 months, and 7.1 months for the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively. There was no statistical difference in the primary end point of PFS between the olaparib and PLD groups, and the ORR for olaparib 400 mg was consistent with that found in other studies. The PFS for the PLD group was better than that noted in a prior study.

The next study was a double-blind, placebo-controlled phase 2 study examined the efficacy of maintenance therapy with single-agent olaparib in women with platinum-sensitive recurrent ovarian cancer. The criteria for eligibility included a partial or complete response to the last course of platinum-based chemotherapy; *BRCA* testing was not a requirement for enrollment.[86] The primary endpoint was PFS measured by RECIST criteria. Women randomly assigned to the olaparib group clearly demonstrated improvement of PFS from 4.8 to 8.4 months (HR 0.35, $P < 0.001$), although no OS benefit was observed. Within the subgroup analysis, the patients treated with olaparib demonstrated a lower risk of progression compared with placebo.

The follow-up study was a preplanned retrospective analysis of outcomes by *BRCA* status. When the degree of effect was evaluated in women with *BRCA*-related ovarian cancer, the improvement in PFS increased from 4.3 to 11.2 months, demonstrating that patients with *BRCA* mutations definitely show response to a PARP inhibitor.[87] There was no significant benefit noted in OS, but 23% of the patients with *BRCA* mutations who were in the placebo group and who were eligible for additional treatment received a PARP inhibitor post-progression. Based upon this observation, several phase 3 trials examining the role of PARP inhibitors as maintenance therapy were designed.[88] SOLO 1, now closed to accrual, was opened in April 2013 and recruited participants who had *BRCA* mutation and completed first-line platinum-based chemotherapy. PFS is the primary outcome measure. SOLO 2, also closed to accrual, is a phase 3 randomized double-blind placebo-controlled study of olaparib maintenance monotherapy in platinum-sensitive relapsed *BRCA*-positive women with clinical response or partial response following platinum-based chemotherapy. SOLO 3 is currently recruiting *BRCA*-positive women who have progressed after at least 6 months after their last platinum treatment and have received at least 2 prior platinum treatments. The FDA approved

olaparib (Lynparza) as a treatment for patients with documented *BRCA* mutation in ovarian carcinoma in December 2014. Additional studies are ongoing evaluating other PARP inhibitors.

Olaparib is also being studied in combination with agents that target other molecular pathways such as cediranib (an oral anti-angiogenic agent against VEGF receptor). A randomized phase 2 study with olaparib and cediranib versus olaparib alone in platinum-sensitive women with ovarian cancer has been reported. The median PFS was 17.7 months in the combination arm compared with 9.0 months in the olaparib-alone arm (HR 0.42, $P = 0.005$).[89] In women with platinum-sensitive high-grade serous or endometrioid ovarian cancer, there was an improved PFS.

AKT pathway activation is common in high-grade serous ovarian cancers and is therefore sensitive to selective AKT targeting.[90] Molecular alterations in the PI3K/Akt pathway are associated with platinum-resistance and are an area of ongoing study.[91] Additionally, clinical trials testing dual inhibitors such as olaparib and PI3K inhibitors are in progress,[92] as are studies to further define the genomic similarities between basal-like breast cancer and high-grade serous ovarian tumors.[93]

Other Agents Targeting Molecular Pathways

Low-grade serous carcinoma (LGSC) accounts for less than 20% of ovarian cancers and is molecularly different from the high-grade group. Mutations which are commonly found in LGSC are *KRAS*, *BRAF*, and *ERBB2* which can then activate the MAP kinase pathway.[94] These tumors are typically refractory to cytotoxic chemotherapy. A single-arm phase 2 study with selumetinib (MAP kinase inhibitor MEK 1/2) showed a high rate of disease stabilization and a median PFS of 11 months.[95] Presently, GOG 281 is a phase 2/3 randomized trial comparing trametinib with standard treatment in recurrent or progressive low-grade serous ovarian or peritoneal cancer. It is actively accruing.

Studies have evaluated the folate receptor since it is expressed in more than 90% of ovarian subtypes, and higher expression may be associated with a poorer prognosis.[96] The PRECEDENT study was a randomized phase 2 trial comparing EC145 (vintafolide) with PLD in combination versus PLD alone in platinum-resistant ovarian cancer.[97] The combination therapy demonstrated improvement over standard therapy in patients with 100% of lesions positive for folate receptor. The median PFS was 5.5 months compared with 1.5 months with PLD alone (HR 0.38, $P = 0.013$). Unfortunately, the phase 3 study was stopped based on the data and at the recommendation of the safety monitoring board since the PFS was not improved in the study arm.

Anti-angiogenic agents, which target blood vessel growth, have demonstrated single-agent activity in ovarian cancer, with reported response rates of 16% to 21% for bevacizumab, a monoclonal anti-VEGF antibody,[98,99] and 17% for cediranib, an oral tyrosine kinase inhibitor of VEGF receptor.[100] Other oral targeted agents such as sorafenib, sunitinib, and pazopanib are being studied in ongoing trials. The incidence of hypertension with these oral anti-angiogenic agents is higher than that for bevacizumab.

The angiopoietin axis is another target and trebananib (AMG 386), a peptide inhibiting the interaction of angiopoietin 1 and 2 with their Tie2 receptors, is also being studied. The phase 3 trial TRINOVA-3 (AMG 386 versus placebo with carboplatin/paclitaxel) has recently closed accrual with results pending [NCT01493505].

Although epidermal growth factor receptor (EGFR) is overexpressed in approximately 70% of ovarian cancer patients, response to EGFR inhibitors is infrequent in this population; however, there may be a synergy with the PI3K pathway.[101]

Insulin-like growth factor (IGF-1) is thought to be involved in the etiology of epithelial cancers, including ovarian cancer.[102] IGF-1 is involved in cellular proliferation, invasion, and angiogenesis in epithelial ovarian cancer.[103] The most recent investigations have noted IGF-1 overexpression in low-grade but not high-grade serous ovarian cancer cell lines. The European Prospective Investigation into Cancer and Nutrition (EPIC) study is investigating the role of IGF-1 and ovarian cancer risk.[104]

Ganitumab (AMG 479) is a human monoclonal antibody against IGF-IR, another molecular pathway involved in the pathogenesis of ovarian cancer. Ganitumab has been recommended for testing as either a single agent or in combination with standard chemotherapy.[105]

Immune therapies are being studied as well, including the agent nivolumab, which is an antibody that targets programmed cell death-1 (PD-1) receptor and prevents interaction with its ligand (PD-L1). This inhibition enables activation of T cells against tumor cells. A phase 2 study reported a response in advanced platinum-resistant ovarian cancer.[106]

CONCLUSION

There are still multiple challenges remaining in the diagnosis and treatment of epithelial ovarian cancer. However, with the ongoing molecular research identifying specific targets, therapies will become more directed and less toxic. Also, molecular studies may aid in early diagnosis and possibly translate into a better overall prognosis for these women.

BOARD REVIEW QUESTIONS

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REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
2. Salani R, Santillan A, Zahurak ML, et al. Secondary cytoreductive surgery for localized, recurrent epithelial ovarian cancer: analysis of prognostic factors and survival outcome. Cancer. 2007;109:685–691.
3. Raja FA, Chopra N, Ledermann JA. Optimal first-line treat¬ment of ovarian cancer. Ann Oncol 2012;23(suppl 10): x118–27.
4. Berlin S, Liu JF. Epithelial ovarian cancer: evaluation, staging, surgery, and stage I and II disease management. Hospital Physician Oncology Board Review Manual. Volume 11, Part 2. March 2015.
5. NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Including fallopian tube cancer and primary peritoneal cancer. Version 1.2015. http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed April 30, 2015.
6. 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.
7. 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.
8. Armstrong DK, Bundy B, Wenzel L, et al; Gynecologic Oncology Group. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N England J Med 2006;354:34–43.
9. National Cancer Institute. NCI Clinical Announcement: Intraperitoneal chemotherapy for ovarian cancer. May 1, 2006. http://ctep.cancer.gov/highlights/docs/clin_annc_010506.pdf. Accessed April 22, 2015.
10. Jaaback K, Johnson N. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database Syst Rev 2006(1):CD005340.
11. Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database Syst Rev 2011;(11):CD005340.
12. Landrum LM, Java J, Mathews CA, et al. Prognostic factors for stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy: a Gynecologic Oncology Group study. Gynecol Oncol 2013;130:12–18.
13. Tewari D, Java JJ, Salani R, et al. Long-term survival ad-

vantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol.
14. 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.
15. ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. ICON Collaborators. International Collaborative Ovarian Neoplasm Study. Lancet 1998;352:1571–6.
16. 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 Clinical Oncology 2003;21:3194–200.
17. du Bois A, Luck HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003;95:1320–9.
18. International Collaborative Ovarian Neoplasm Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin and cisplatin in women with ovarian cancer: the ICON 3 randomized trial. Lancet 2002;360(9332):505–15.
19. 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.
20. 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.
21. Burger RA, Brady MF, Bookman MA, et al; Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473–83.
22. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484–96.
23. Aravantinos G, Pectasides D. Bevacizumab in combination with chemotherapy for the treatment of advanced ovarian cancer: a systematic review. J Ovarian Res 2014; 7:1-13.
24. Raja FA, Chopra N, Ledermann JA. Optimal first-line treatment of ovarian cancer. Ann Oncol 2012;23(suppl 10):x118–27.
25. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007; 25:5165–71.
26. Garcia AA, Hirte H, Fleming G, Yang D, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. J Clin Oncol 2008;26:76–82.
27. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32:1302–8.
28. 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.
29. Katsumata N. Dose-dense therapy is of benefit in primary treatment of ovarian cancer? In favor. Ann Oncol 2011;22 Suppl 8:viii29–viii32.
30. Bonilla L, Ben-Aharon I, Vidal L, et al. Dose-dense chemotherapy in nonmetastatic breast cancer: a systemic review and meta-analysis of randomized control studies. J Natl Cancer Inst 2010;102:1845–54.
31. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomized controlled trial. Lancet 2009;374:1331–8.
32. 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 randomized, controlled, open-label trial. Lancet Oncol 2013;14:1020–6.
33. van der Burg ME, Boere IA, Berns PM. Dose-dense therapy is of benefit in primary treatment of ovarian cancer: contra. Ann Oncol 2011;22 (suppl 8):33–39.
34. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicenter, open-label, phase 3 trial. Lancet Oncol 2014;15:396–405.
35. Monk BJ, Huang H, Penson SA, et al. Health-related quality of life associated with every-3-week paclitaxel vs dose-dense weekly paclitaxel in combination with carboplatin with or without bevacizumab for primary ovarian cancer: Gynecologic Oncology Group study 262. (Abstract) Gynecol Oncol 2014;133:58 (SGO #139).

36. Vergote I, Tropé CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943–53.
37. Schmeler KM, Sood AK, Bell-McGuinn KM, et al. Proceedings from the 9th International Conference on Ovarian Cancer. Gynecol Oncol 2012;125:5–7.
38. Vergote I, du Bois A, Amant F, et al. Neoadjuvant chemotherapy in advanced ovarian cancer: On what do we agree and disagree? Gynecol Oncol 2013;128:6–11
39. Onda T, Yoshikawa H, Shibata T, et al. 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 phase III randomized trial: JCOG0602. ASCO Annual Meeting. Abstract 5508. J Clin Oncol 2014;32:5s (suppl; 5508).
40. Onda T, Yoshikawa H, Shibata T, et al. 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 phase III randomized trial: JCOG0602. J Clin Oncol 32:5s 2014 (suppl; abstr 5508).
41. 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.
42. Hakes TB, Chalas E, Hoskins WJ, et al. Randomized prospective trial of 5 versus 10 cycles of cyclophosphamide, doxorubicin and cisplatin in advanced ovarian carcinoma. Gynecol Oncol 1992;45:284–9.
43. Bertelsen K, Jakobsen A, Strøyer J, et al. A prospective randomized comparison of 6 and 12 cycles of cyclophosphamide, doxorubin and cisplatin and advanced ovarian cancer; A Danish Ovarian Study Group Trial: (DACOVA). Gynecol Oncol 1993;49:30–6.
44. Barakat RR, Almadrones L, Venkatraman ES, et al. A phase II trial of intraperitoneal cisplatin and etoposide as consolidation therapy in patients with Stage II-IV epithelial ovarian cancer following negative surgical assessment. Gynecol Oncol 1998;69:17–22.
45. Piccart MJ, Floquet A, Scarfone G, et al Interperitoneal cisplatin versus no further treatment: 8 year results of EORTC 55875, a randomized phase III study in ovarian cancer patients with a pathologically complete remission after platinum-based intravenous chemotherapy. Int J Gynecol Cancer 2003;13 suppl 2:196–203.
46. Gynecologic Oncology Group. Paclitaxel or Polyglutamate Paclitaxel or Observation in Treating Patients With Stage III or Stage IV Ovarian Epithelial or Peritoneal Cancer. www.clinicaltrials.gov/ct/gui/show/NCT00108745?order=1. Accessed April 24, 2015.
47. Hurteau JA. Randomized phase III trial of tamoxifen versus thalidomide in women with biochemical-recurrent-only epithelial ovarian, fallopian tube or primary peritoneal carcinoma after a complete response to first-line platinum/taxane chemotherapy with an evaluation of serum vascular endothelial growth factor (VEGF): A Gynecologic Oncology Group Study. Gynecol Oncol 2010;119:444–50.
48. Rustin GJ, van der Burg ME, Griffith CL, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomized trial. Lancet 2010;376:1155–63
49. Chi DS, McCaughty K, Diaz JP, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. Cancer 2006;106:1933–9.
50. A trial looking at surgery for ovarian cancer that has come back (DESKTOP 3). Cancer Research UK website. www.cancerresearchuk.org/about-cancer/trials/a-trial-looking-surgery-ovarian-cancer-that-come-back-desktop-3. Accessed April 24, 2015.
51. Carboplatin, Paclitaxel and Gemcitabine Hydrochloride With or Without Bevacizumab After Surgery in Treating Patients With Recurrent Ovarian Epithelial Cancer, Primary Peritoneal Cavity Cancer, or Fallopian Tube Cancer. National Cancer Institute website. www.cancer.gov/clinicaltrials/search/view?cdrid=546714&version=HealthProfessional. Accessed April 24, 2015.
52. van de Laar R, Zusterzeel PL, Van Gorp T, et al. Cytoreductive surgery followed by chemotherapy versus chemotherapy alone for recurrent platinum-sensitive epithelial ovarian cancer (SOCceR trial): a multicenter randomised controlled study. BMC Cancer 2014;14:22. doi: 10.1186/1471-2407-14-22.
53. Lee CK, Lord S, Grunewald T, et al. Impact of secondary cytoreductive surgery on survival in patients with platinum sensitive recurrent ovarian cancer: analysis of the CALYPSO trial. Gynecol Oncol 2015; 136:18–24.
54. Kucukmetin A, Naik R, Galaal K, et al. Palliative surgery versus medical management for bowel obstruction in ovarian cancer. Cochrane Database Syst Rev 2010 Jul 7;(7):CD007792.
55. Markman M, Rothman R, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J Clin Oncol 1991;9:389–93.
56. Markman M, Markman J, Webster K, et al., Duration of response to second-line, platinum-based chemotherapy for ovarian cancer: implications for patient management and clinical trial design. J Clinical Oncol 2004 22: 3120–5.

57. Gore ME, Fryatt I, Wiltshaw E, et al. Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. Gynecol Oncol 1990;36:207–11.
58. Bolis G, Scarfone G, Giardina G, et al; Associazione per la Ricerca in Ginecologia Oncologia (ARGO 96) Study Group.. Carboplatin alone vs carboplatin plus epidoxorubicin as second-line therapy for cisplatin- or carboplatin-sensitive ovarian cancer. Gynecol Oncol 2001;81:3–9
59. Zanotti KM, Belinson JL, Kennedy AW, et al. Treatment of relapsed carcinoma of the ovary with single-agent paclitaxel following exposure to paclitaxel and platinum employed as initial therapy. Gynecol Oncol 2000;79:211–5.
60. ten Bokkel Huinink W, Gore M, Carmichael J, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol 1997;15:2183–93.
61. Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma: A randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001;19:3312–22.
62. Parmar MK, Ledermann JA, Colombo N; 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.
63. Thigpen T. Design issues in clinical trials of ovarian carcinoma. www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm120669.pdf. Accessed May 14, 2015.
64. Gonzalez-Martin AJ, Calvo E, Bover I, et al., Randomized phase II trial of carboplatin versus paclitaxel and carboplatin in platinum-sensitive recurrent advanced ovarian carcinoma: a GEICO (Grupo Espanol de Investigacion en Cancer de Ovario) study. Ann Oncol 2005;16:749–55.
65. Pfisterer J, Vergote I, Du Bois A, et al; AGO/OVAR; NCIC CTG; EORTC GOG. Combination therapy with gemcitabine and carboplatin in recurrent ovarian cancer. Int J Gynecol Cancer 2005;15 Suppl 1:36–41.
66. Pujade-Lauraine E, Mahner S, Kaern J, et al. A randomized, phase III study of carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in relapsed platinum-sensitive ovarian cancer (OC): CALYPSO study of the Gynecologic Cancer Intergroup (GCIG). J Clin Oncol 2009; 27(18s):suppl; abstr LBA5509.
67. 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 2012. Br J Cancer 2012;107:588-91.
68. Friedlander M, Millward MJ, Bell D, et al. A phase II study of gemcitabine in platinum pre-treated patients with advanced epithelial ovarian cancer. Ann Oncol 1998;9:1343–5.
69. Sorenson P, Hoyer M, Jakobsen A, et al. Phase II study of vinorelbine in the treatment of platinum-resistant ovarian carcinoma. Gynecol Oncol 2001;81:58–62.
70. Rose PG, Blessing JA, Mayer AR, et al. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 1998;16:405–10.
71. Bodurka DC, Levenback C, Wolf JK, et al. Phase II trial of irinotecan in patients with metastatic epithelial ovarian cancer or peritoneal cancer. J Clin Oncol 2003;21: 291–7.
72. Miller DS, Blessing JA, Krasner CN, et al. Phase II evaluation of pemetrexed in the treatment of recurrent or persistent platinum-resistant ovarian or primary peritoneal carcinoma: a study of the Gynecologic Oncology Group. J Clin Oncol 2009;27:2686–91
73. Francis P, Schneider J, Hann L, et al. Phase II trial of docetaxel in patients with platinum-refractory advanced ovarian cancer. J Clin Oncol 1994;12:2301–8.
74. Markman M, Hakes T, Reichman B, et al. Ifosfamide and mesna in previously-treated advanced epithelial ovarian cancer: activity in platinum-resistant disease. J Clin Oncol 1992;10:243–8.
75. Pujade-Lauraine E, Hilpert F, Weber B, et al; AURELIA Investigators. AURELIA: A randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC). ASCO Annual Meeting 2012. J Clin Oncol 2012;30 (suppl; abstr LBA5002).
76. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005;434(7035):913–7.
77. Farmer HH, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434(7035):917–21.
78. Sessa C. Update on PARP 1 inhibitors in ovarian cancer. Ann Oncol 2011;22 (suppl 8):72–6.
79. Venkitaraman AR. A growing network of cancer-susceptibility genes. N Engl J Med 2003;348:1917–9.
80. Rouleau M, Patel A, Hendzel MJ. PARP inhibition: PARP and beyond. Nat Rev Caner 2010;10:293–301.
81. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123–34.
82. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 2011;12:852–61.
83. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with

BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 2010;376(9737):245–51.
84. Del Conte G, Sessa C, von Moos R, et al. Phase I study of olaparib in combination with Liposomal doxorubicin in patients with advanced cancers. Br J Cancer 2014;111:651–9.
85. Kaye SB, Lubinski J, Matulonis U, et al. Phase II, open-label, randomized, multicnetered study comparing the efficcacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegulated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol 2012;30:372–9.
86. 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.
87. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (SOC) and a BRCA mutation (BRCAm). Lancet Oncol 2014;15:852-–61.
88. Moore KN, DiSilvestro P, Lowe E, et al. SOLO1 and SOLO2: randomized phase III trials of olaparib in patients with ovarian cancer and a BRCA1/2 mutation. 2014 ASCO Annual Meeting. J Clin Oncol 32:5s poster session. Abstract TPS5616. http://meetinglibrary.asco.org/content/98501.
89. 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.
90. Hanrahan AJ, Schultz N, Westfal ML, et al. Genomic complexity and AKT dependence in serous ovarian cancer. Cancer Discov 2012;2:56–67.
91. Zhang L, Huang J, Yang N, et al. Integrative genomic analysis of phosphatidylinositol 3'-kinase family identifies PIK3R3 as a potential therapeutic target in epithelial ovarian cancer. Clin Cancer Res 2007;13(18 Pt 1): 5314–21.
92. Phase I Study of the Oral PI3kinase Inhibitor BKM120 or BYL719 and the Oral PARP Inhibitor Olaparib in Patients With Recurrent Triple Negative Breast Cancer or High Grade Serous Ovarian Cancer. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT01623349. Accessed April 30, 2015.
93. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors. Nature 2012;490:61–70.
94. Lopez J, Banerjee S, Kaye SB. New developments in the treatment of ovarian cancer- future perspectives. Ann Oncol 2013;24(supp 10):69–76.
95. Farley J, Brady WE, Vathipadiekal V, et al. Selumetrinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open label, single-arm, phase 2 study. Lancet Oncol 2013;14:134–40.
96. O'Shannessy DJ, Somers EB, Smale R, Fu YS. Expression of folate receptor-alpha (FRA) in gynecologic malignancies and its relationship to the tumor type. Int J Gynecol Pathol 2013;32:258-–68
97. Naumann RW, Coleman RL, Burger RA, et al. PRECEDENT: a randomized phase II trial comparing vintafolide (EC145) and Pegylated Liposomal Doxorubicin (PLD) in combination versus PLD alone in patients with platinum-resistant ovarian cancer. J Clin Oncol 2013;31:4400–6.
98. Cannistra SA, Matulonis UA, Penson RT, Hambleton J, Dupont J, Mackey H, Douglas J, Burger RA, Armstrong D, Wenham R, McGuire W, Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer of peritoneal serous cancer. J Clin Oncol 2007;25:180–6.
99. Burger RA, Brady MF, Bookman MA, et al; Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473–83.
100. Matulonis UA, Berlin S, Ivy P, et al. Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. J Clin Oncol 2009;27:5601–6.
101. Glaysher S, Bolton LM, Johnson P, et al. Targeting EGFR and PI3K pathways in ovarian cancer. Br J Cancer 2013;109:1786–94.
102. Singh P, Alex JM, Bast F. Insulin receptor (IR) and the insulin-like growth factor receptor I (IGF-IR) signaling systems: novel treatment strategies for cancer. Med Oncol 2014;31:805.
103. Beauchamp MC, Yasmeen A, Knafo A, Gotlieb WH. Targeting insulin and insulin-like growth factors pathways in epithelial ovarian cancer. J Oncol 2010;2010:257058.
104. Ose J, Fortner RT, Schock H, et al. Insulin-like growth factor I and risk of epithelial invasive ovarian cancer by tumour characteristics: results from the EPIC cohort. Br J Cancer 2015;112:162–6.
105. Beltran PJ, Calzone FJ, Mitchell P, et al. Ganitumab (AMG 479) inhibits IGF-II dependent ovarian cancer cell growth and potentiates platinum-based chemotherapy. Clin Cancer Res 2014;20:2947–58.
106. Hamanishi J, Mandai M, Ikeda T, et al. Efficacy and safety of anti PD-1 antibody (Nivolumab: BMS-936558, 0N0-4538) in patients with platinum-resistant ovarian cancer. 2014 ASCO Annual Meeting. J Clin Oncol 2014;32:5s (suppl; abstr 5511).