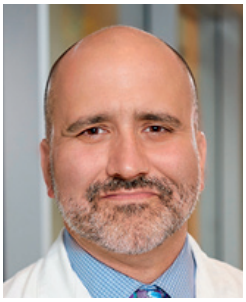
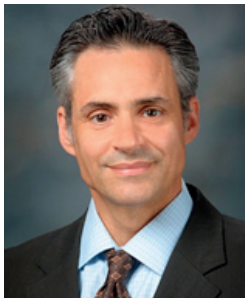
Chapter 4 |

The GOG Foundation, Inc. Ovarian Cancer Trials

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Introduction

The GOG Foundation, Inc. (GOG-F) has an extensive history of research in ovarian cancer, with the results of many of its clinical trials establishing the standard of care for treatment of this disease both in the United States and internationally. These trials have addressed the role of staging, surgery and treatment in ovarian cancer. Historically, treatment trials have been distributed by stage, amount of residual disease and cell type. More recently, ovarian cancer clinical trials have evolved to inorporate insight into the molecular mechanisms of certain cell types and the prevalence of newer targeted strategies. The purpose of this chapter is to review the ovarian cancer trials of the GOG-F from its inception to the present day. In order to demonstrate the progression of the GOG-F experience in an orderly fashion, we have divided the GOG experience into early stage epithelial ovarian cancer (EOC), advanced stage (EOC), rare tumors of the ovary, and other trials in ovarian cancer.

Early Stage Ovarian Cancer

Protocol 1 was activated in 1971 and closed to patient entry in 1978. [1] Eligible patients with stage I epithelial ovarian cancer following surgical therapy were randomized to one of three groups: 1) no further therapy; 2) pelvic irradiation (5000 cGy over five to six weeks); or 3) melphalan chemotherapy (oral dosage of 0.2 mg per kg daily for five days every four weeks for 18 months). Patients with tumors of low malignant potential and patients with ascites were excluded. One hundred sixty-eight patients were enrolled and 86 were evaluable. Recurrence of cancer by type of therapy was 17% for the no further therapy arm; 30% for the irradiation arm; and 6% for the chemotherapy arm. Recurrence was also related to grade (grade 1: 11%, grade 2: 22%, grade 3: 27%) and to substage (IA1 – 10%, IB2 – 50%). The authors concluded that with the exception of IA1 tumors, patients with stage I cancers of the ovary are best managed by melphalan chemotherapy. They further concluded the patients could only be classified as stage IA1 if they underwent a full surgical staging operation. [1]

However, the use of an alkylating agent was not without adverse sequelae. In 1982, the National Cancer Institute (NCI) Epidemiology Branch published a follow-up report on the patients treated in this study as well as patients treated with alkylating agent chemotherapy at M.D. Anderson Hospital and Princess Margaret Hospital. Nine hundred and ninety-eight patients treated with alkylating agent chemotherapy, twelve cases of acute nonlymphocytic leukemia occurred in these patients compared to an expected number of 0.11. [2]

In 1976, two collaborative clinical trials began to further evaluate the treatment of early stage ovarian cancer. These trials started as studies of the Ovarian Cancer Study Group (composed of physicians from the Mayo Clinic, the M. D. Anderson Hospital and Tumor Institute, the NCI, and the Roswell Park Memorial Institute) and in 1978 were joined by the Gynecologic Oncology Group (GOG). GOG 7601 (number assigned when the GOG joined the study) enrolled stage IA1 and stage IB1 (well and moderately differentiated) EOC randomizing patients to no further therapy versus melphalan chemotherapy (0.2 mg/kg orally days one to five on a 28-day cycle for 12 courses or 18 months). GOG protocol 7602 randomized patients with stage IC and stage IIA, B, C, and selected stage IA2 and IB2 to either melphalan chemotherapy (as

above) or intraperitoneal P32 (chromic phosphate) at a dose of 15 mCiIn. In protocol 7601, with median follow-up of more than six years, there was no significant difference in either disease-free survival (DFS) (P=0.41) or overall survival (OS) (P=0.43). The five-year survival rate was 94% for the no treatment arm and 98% for the melphalan arm. For protocol 7602, after follow-up of more than six years in surviving patients, there was no difference in DFS (P=0.48) and OS (P=0.87). The five-year survival for the melphalan arm was 81% and, for 32P, it was 78%. The authors concluded that patients with stage IA1 and IB1 well or moderately differentiated tumors that are well staged surgically do not benefit from additional treatment. For other early-stage patients, treatment is indicated, but there is no clear difference in benefit for either melphalan or intraperitoneal P32.[3]

Building on the results of GOG 7602, the GOG opened protocol 95 in 1986 as a prospective randomized trial of intraperitoneal P32 compared with cyclophosphamide/cisplatin combination chemotherapy in women with early-stage EOC at high risk for recurrence.[4] Eligibility included surgically-staged patients with stage IA grade 3, IB grade 3, stage IC, or completely resected stage II EOC. A total of 251 patients were randomized to either intraperitoneal (IP) P32 or cisplatin/cyclophosphamide (CP) chemotherapy between the years 1986 and 1994. The cumulative incidence of recurrence at 10 years was 35% for patients receiving IP P32 and 28% for those receiving CP (p=0.15). The death rate for patients treated with CP was 17% lower than for patients treated with IP P32. The authors concluded that although there were no statistically significant differences in survival, the lower cumulative recurrence seen with CP and the increased toxicity of IP P32 administration made the platinum-based combinations the preferred adjuvant therapy for early EOC. 4 This trial was important in introducing cisplatin based chemotherapy to the treatment of EOC.

Building upon the demonstrated efficacy of paclitaxel in more advanced stage clinical trials, GOG #157 compared carboplatin (AUC 7.5) and paclitaxel (175 mg/m2) for three cycles as the control arm versus six cycles of the same drugs as the experimental arm using the same high-risk criteria of surgically-staged patients in an effort to define the optimal duration of therapy. Between 1995 and 1998, 457 eligible patients were enrolled in this study and the results were reported after a median duration of follow-up of 6.8 years. The recurrence rate was 24% lower with six versus three cycles (p=0.18) in this study powered for a 50% reduction. The overall death rate was similar for these two regimens with a hazard ratio of 1.02. Of note, the patients who had the six-cycle regimen experienced 11% grade 3 or 4 neurotoxicity versus 2% in the three cycle regimen. The authors concluded that compared to three cycles, six cycles of carboplatin/paclitaxel did not significantly alter the recurrence rate in high-risk, early-stage EOC, but was associated with more toxicity. [5] The interpretation and application of this study has been the source of controversy and editorials. 6,7-serous cancers (25% endometrioid; 7% mucinous; 30% clear cell; 10% mixed, 5% other), the serous cancers showed a significantly decreased risk of recurrence following six compared to three cycles of chemotherapy (HR=0.33, 99% CI=0.14–0.77; p=0.007). The benefit of three additional cycles of chemotherapy was not evident in non-serous tumors (HR=0.94, 99% CI=0.60–1.49; p=0.806), nor in either of the subsets. These results were maintained after adjusting for confounding variables. The difference in two and five year PFS was improved in the serous cancers with six cycles of chemotherapy (two-year 81% vs 93% and five-year 60% vs. 83% in serous cancer with six versus three cycles respectively) (REF in comments).[71]

Further analysis of high-risk, early-stage ovarian cancer patients in GOG 95 and 157 indicated that a disproportionately large percentage of recurrences were coming from the stage II group. Indeed, GOG 95 reported that the 10-year cumulative incidence of recurrence for stage I patients was 27%; however, this increased to 44% for stage II patients (p=0.01). Similar data was seen for GOG 157. Based on this compelling data, the GOG opted to remove stage II patients from future protocols analyzing early-stage, high-risk disease and, instead, included these patients into trials with advanced-stage patients.[5]

The most recent trial for high-risk, early-stage EOC was GOG 175. Based on the theory that low dose therapy with paclitaxel has anti-angiogenic properties, this trial randomly assigned patients to three cycles of paclitaxel (175 mg/meter squared) and carboplatin (AUC 6) chemotherapy with or without 24 weekly doses of paclitaxel (40 mg/meter squared) maintenance chemotherapy. This trial enrolled 571 patients of which 542 were evaluable for the study endpoints from 1998 to 2006. The patient population was similar to GOG 157 with 28% of patients having serous and 72% other histologies (21% endometrioid, 6% mucinous, 31% clear cell, 2%a adenocarcinoma NOS, 10% mixed and 2% other). There was no additional benefit in the risk of recurrence and overall survival at 5 years with the addition of maintenance paclitaxel.[8] There were higher rates of peripheral neuropathy, infection/fever and dermatologic events with the addition of maintenance paclitaxel.[72]

GOG 175 represents the most recent trial for treatment

of women with high risk, early stage ovarian cancer. At the time of this publication, there are no active treatment trials in this patient population. Identifying and Improving the outcomes in early stage patients who are at the highest risk of recurrence continues to be an opportunity, especially with the development of molecularly targeted therapies (e.g. PARP inhibitors).

Advanced Epithelial Ovarian Cancer

Historically, the GOG separated patients with advanced stage EOC into optimally debulked or suboptimally debulked populations after GOG trial #2. This was based on many publications demonstrating an increase in PFS and OS based on the amount of residual disease at the time of surgical cytoreduction (CRS). The strict definition of optimal debulking changed over time as demonstrated in the inclusion criteria of the following studies, with a stricter definition of smaller residuals as optimally debulked over time. Ultimately, changes in strategy towards cell type driven treatment and the advent of targeted therapy, has led to inclusion of both optimally and suboptimally debulked patients together in GOG advanced stage ovarian cancer clinical trials to be discussed later in this review.

GOG 2 opened in 1970 and closed in 1976. Eligible patients were patients with stage III EOC (low-malignant potential excluded) and they were stratified into optimal residual disease (<3 cm or less) and suboptimal residual disease (> 3 cm). 9 Randomization was to one of four treatment arms: 1) whole abdominal irradiation alone (2000 to 2500 cGy over 3 to 4 weeks); 2) whole abdominal irradiation (as above) followed by melphalan chemotherapy (0.2mg/kg daily for five days every four weeks for 18 months); 3) melphalan chemotherapy alone (dosed as above); and 4) melphalan chemotherapy (as above) followed by whole abdominal irradiation (as above). Progression-free (PFS) and OS for the optimal group of patients was 11.8 months and 28.5 months; for the suboptimal group of patient's PFS was 7.3 months; OS was 15.7 months. The authors concluded that PFS appeared better with combined modality therapy but due to small numbers it was not statistically significant. OS was not different.[9]

GOG 3 evaluated stage IV primary ovarian cancer and recurrent ovarian cancer equivalent to stage III or IV.[24] Randomization was to one of four arms: 1) Melphalan (0.2 mg/kg/day for five days every four weeks for 18 months; 2) Melphalan (as dosed above) plus 5-fluorouracil 15 mg/kg/day for five days every four weeks; 3) Melphalan and 5-fluorouracil as dosed above plus dactinomycin 0.5 mg daily for five days every four weeks; and 4)Cytoxan (7 mg/kg/day), 5-fluorouracil (as dosed above) and dactinomycin (as dosed above). Four hundred and twenty-seven patients were in the study, 314 of whom are evaluable. The fourth arm was discontinued due to toxicity. There was no significant difference in either progression-free or overall survival between any of the treatment arms. Toxicity was greatest in the three drug regimens. The authors concluded that single agent melphalan was as efficacious as any of the combination regimens in advanced/recurrent epithelial ovarian cancer.[24, 73]

GOG protocol 22 opened in 1976 and closed in 1979.[25] This protocol was carried out in suboptimally debulked (residual tumor diameter of >3 cm) stage III, stage IV and recurrent EOC and randomized patients to melphalan (7 mg/m2 orally for 5 days every 4 weeks) for 18 months versus melphalan (dose as above) plus hexamethylmelamine (150 mg/m2 daily for 14 days every four weeks) versus Adriamycin (50 mg/m2 every 3 weeks) for nine cycles plus cyclophoosphamide (500 mg/m2 intravenously every three weeks which was escalated by 25% when Adriamycin was stopped) for 18 months. During the study period, 432 patients were randomized into this trial. After twoand-one-half years, an interim analysis indicated melphalan alone was significantly inferior in achieving clinical complete responses and the GOG elected to close that arm to patient entry.[74]

Although there was a trend towards improved complete and overall response in the combination chemotherapy arms, this was not statistically significant in the patients with measurable disease. Also PFS was not significantly different (median = 7.7 months, M+H = 6.0 months and A+C = 9.5 months). Overall survival was also similar (median = 12.3 months, M+H = 13.5 months and A+C = 14.2 months). [25]

In 1979, the GOG opened its first phase III trial of cisplatin in advanced epithelial ovarian cancer. This trial, GOG 47, evaluated cyclophosphamide (500 mg/m') and doxorubicin (50 mg/m2) with or without cisplatin (50 mg/m2) every three weeks for eight courses over six months (CAP vs CA).[26] A second look laparotomy was performed in patients with a complete response and in patients with non-measurable disease without progression. If no evidence of disease was found at exploration or if all residual disease could be resected, the patient received IV cyclophosphamide alone every three weeks, escalating from 500 mg/m2 to maximum-tolerated doses (no more than 1,100) mg/m2 per dose) until relapse or for a total of 12 months after the second-look surgery. This trial closed in 1982, having accrued 440 evaluable patients with stage III suboptimal (>3 cm), stage IV and recurrent cancer. For

patients with measurable disease, the response rate for CA was 26% (CR) and 48% (CR + PR), while for CAP it was 51% (CR) and 76% (CR + PR). The difference in complete response rate was highly statistically significant (P<0.0001).26 The authors concluded that because of the clear improvement in response rate and PFS in all patients and OS rate for patients with measurable disease, cisplatin-based therapy is a "significant step forward" in the therapy of EOC. They expressed confusion as to the lack of a statistically significant OS in the entire group of patients, indicating the possible reasons being some imbalance in the arms or, more likely, the result of crossover therapy to cisplatin in patients whose tumors progressed on the non-cisplatin arm.[26]

In 1991, Omura et al.[27] published the long term follow-up and prognostic factors of patients treated on GOG protocols 22 and 47. There were 319 patients evaluable for protocol 22 and 407 evaluable patients for protocol 47. All patients were suboptimal (3cm or greater) stage III or stage IV. Almost 60% had measurable disease. They found cell types other than clear cell and mucinous, good performance status, cisplatin-based therapy, younger age, lower stage, smaller residual tumor and absence of ascites to be favorable prognostic factors. Second look surgery was more often negative in endometrioid tumors (P<0.05) and of the 30 patients with suboptimal stage III who had a negative second-look, 18 (60%) recurred and 13 (43%) died.[27, 75]

Evaluation of cisplatin in optimally debulked advanced stage EOC began with GOG 52. GOG #52 compared cyclophosphamide (1,000 mg/m2) plus cisplatin (50 mg/m2) with or without doxorubicin (50 mg/m2) every three weeks for eight cycles (CP vs CAP) in front line therapy.[12] This protocol used what was to become the GOG standard for classifying patients as optimal disease for future trials, i.e., residual disease with a maximum diameter of <1 cm. The protocol opened in 1981 and accrued 349 evaluable patients before closing to patient entry in 1985.12 Progression-free interval was approximately 23 months with no significant difference between the two arms (P=0.50). Likewise, there was no significant difference in OS (P=0.24). The authors were able to show statistically significant differences in survival between patients with no gross residual (NGR) versus those with gross residual up to 1 cm and grade 1 tumors versus those with grade 2 or 3.12 The authors concluded that the addition of doxorubicin using dose schedules with equal hematological toxicity in optimal residual stage III has no significant advantage,[76,77]

With the historic division of the EOC population into optimally and suboptimally-debulked tumors, the GOG initiated a sequence of trials looking at suboptimal stage III (> 1 cm residual) or stage IV EOC. GOG 97 study evaluated whether dose intensity of standard chemotherapy improved outcomes in patients with suboptimally debulked EOC. Patients with suboptimally debulked stage III or stage IV ovarian cancer received either eight cycles of cisplatin 50 mg/m2 plus cyclophosphamide 500 mg/m2 or four cycles of cisplatin and cyclophosphamide at 100 mg/m2 and 1000mg/m2, respectively. The more dose intense regimen did not provide improved response rates, PFS or OS. However, a greater toxicity profile was reported with the dose intense regimen.[28, 78]

A secondary analysis of the relationship of the size of the residual disease to outcome revealed that, compared to the group of patients with disease < 2 cm in diameter, all patients with disease > 2 cm—analyzed in 1 cm increments—had a relative risk of dying of between 1.74 and 2.16 with no statistical difference between any of the groups >2 cm.[29, 79]

The GOG was fundamental in the development of paclitaxel as an active agent in EOC. The GOG con- ducted two consecutive, randomized phase III trials assessing the potential value of paclitaxel as first line treatment. The first trial, GOG 111, compared cisplatin and paclitaxel versus cisplatin and cyclophosphamide.The study was opened in April 1990 and closed in March 1992. Eligibility for the trial was all stage III and IV EOC with residual disease > 1 cm. The combined complete and partial clinical response rate for patients with measurable disease favored the paclitaxel arm 77% to 64%. The risk of progression was 28% lower among those patients treated on the paclitaxel arm. The risk of death was 34% lower among those treated with the paclitaxel regimen.[30] The frequency of negative second-look surgery was not statistically different.

However, before the results of that trial were available, the GOG initiated protocol 132 in a similar patient population. This trial was designed to assess whether paclitaxel was more active than cisplatin in the management of EOC.31, 80 GOG 132 was designed to compare the activity in terms of PFS and OS of single-agent cisplatin (100 mg/m2) or paclitaxel (200 mg/m2 over 24 hours) or the combination of cisplatin (75 mg/m2) and paclitaxel (135 mg/m2 over 24 hours). Between 1992 and 1994, 648 eligible patients were enrolled on the trial. The response rate on paclitaxel monotherapy was significantly lower compared with the cisplatin regimen (42% versus 67%). The relative hazard for PFS was significantly greater for those who received cisplatin alone or in combination than those randomized to paclitaxel (relative hazard =

1.41 with a 95% confidence interval of 1.15 to 1.73). The authors concluded that cisplatin alone or in combination with paclitaxel yielded a superior response rate and PFS relative to paclitaxel.[31] In addition, the drug dosages used with the combination therapy had a better toxicity profile; therefore, the combination of cisplatin/paclitaxel was deemed to be the preferred initial treatment option.

The GOG also addressed the role of a second attempt at front line surgical CRS. GOG 152 concentrated on patients with stage III EOC with residual intraperitoneal tumor > 1 cm after they had undergone primary CRS with maximal surgical effort.[32,81] Two weeks after the third cycle of cisplatin/paclitaxel chemotherapy the patients were evaluated for a response by means of physical exam, CT scan and CA-125. Patients whose disease had not progressed and who had residual extraperitoneal of tumor < 1 cm were randomly assigned to receive chemotherapy plus secondary surgical cytoreduction versus chemotherapy alone. From 1994 to 2001, 424 eligible patients were randomized onto this protocol. The likelihood of progression-free survival in the group assigned to secondary surgery plus chemotherapy, as compared with the chemotherapy alone group, was 1.07 with a 95% confidence interval of 0.87 to 1.31 with a p=0.54 and the relative risk of death was 0.99 with a 95% CI of 0.79 to 1.24 with a p=0.92 [32]

These results were in contrast to an EORTC trial reported in the New England Journal of Medicine that showed a significant improvement in both PFS and OS in patients who underwent suboptimal primary debulking followed by secondary surgery. The authors concluded that the difference in the reports was secondary to the nature of the initial surgical effort.[33] In the GOG trial, the patients had an initial attempt at aggressive tumor debulking by a gynecologic oncologist (95%); whereas, this was not a requirement for the European trial. The authors concluded that for a patient with advanced EOC in whom primary CRS was considered to be maximal by a surgeon trained to perform a maximum attempt at tumor reduction (e.g. gynecologic oncologist), the addition of an interval cytoreductive surgery did not improve PFS or OS.[32]

GOG 162 was designed to evaluate the impact of dose schedule on outcome in suboptimally debulked EOC. This was a phase III randomized trial of cisplatin and paclitaxel administered by either a 24-hour (135 mg/m2) or 96-hour (120 mg/m2) infusion in patients with suboptimal stage III or stage IV EOC. From 1996 to 2000, 293 patients were enrolled. Accrual was terminated due to a scheduled interim futility analysis as the median PFS was 12.4 versus 12.6 months for the 24-hour versus 96-hour arm, respectively. The authors concluded that prolonged paclitaxel infusion did not significantly increase duration of survival over a 24-hour infusion.[34, 82]

Following the success of GOG 111, which demonstrated the superiority of paclitaxel combined with cisplatin in ovarian cancer patients with suboptimally debulked advanced disease, the GOG opened GOG 158 comparing carboplatin (AUC 7.5) and paclitaxel (175 mg/m2) over three hours versus cisplatin (75 mg/m2) and a 24-hour infusion of paclitaxel (135 mg/m2).[16] These patients had advanced EOC with no residual mass > 1 cm after surgery. This was designed as a non-inferiority trial. A total of 792 eligible patients were accrued from 1995 to 1998. The relative risk of progression for the carboplatin plus paclitaxel group was 0.88 with a 95% confidence interval of 0.75 to 1.03; the relative risk of death was 0.84 with a 95% confidence interval of 0.72 to 1.02. The authors concluded that for patients with advanced EOC, a chemotherapy regimen consisting of carboplatin plus paclitaxel results in less toxicity, is easier to administer, and is not inferior when compared with cisplatin plus paclitaxel.[16, 83]

The next phase III trial (GOG 182) was designed to examine new active agents in the front-line by incorporating sequential doublet and triplet treatment strategies. The additional agents included pegylated liposomal doxorubicin, gemcitabine and topotecan. In this study, optimally and suboptimally debulked disease were combined in one protocol.[17] This study, designed as a Gynecologic Cancer InterGroup trial, enrolled 4312 women from 2001 to 2004. The patients were randomized to one of five separate regimens. The addition of a third cytotoxic agent provided no benefit in PFS or OS, solidifying carboplatin (AUC 5-6) and paclitaxel (175mg/m2 over three hours) as the backbone and control arm for future GOG trials in patients with advanced stage EOC.[18]

Front Line Maintenance

Despite the advances outlined above, recurrence rates remained high among women diagnosed with advanced EOC and there was an interest in developing strategies and novel agents to use either with and to follow chemotherapy or at the conclusion of chemotherapy to improve oncologic outcomes. The GOG 178/SWOG Intergroup Trial was undertaken to evaluate the concept of maintenance therapy. The study attempted to determine whether continuing paclitaxel for an extended time period in women with advanced EOC, who had a clinically-defined complete response to platinum/paclitaxel based chemotherapy, could prolong subsequent PFS and OS .[50, 84] Patients who were determined to achieve a complete response were assigned to either three or 12

cycles of single-agent paclitaxel at a dose of 175 mg/m2, administrated every 28 days. From 1999 to 2001, 262 eligible patients entered the trial and an interim analysis was performed. The median PFS was 21 and 28 months in the three cycle and 12-cycle paclitaxel arms, respectively (p=.0035).50 With a protocol-specified early termination boundary of p=.005, these findings led to SWOG's Data Safety Monitoring Committee to discontinue the trial and allowed for crossover of the patients treated on the three-cycle arm to the 12-cycle arm. At the time of closure, there was no difference in OS between the treatment arms. It should be noted, however, that there was a high likelihood of crossover for those patients having only received threef cycles of paclitaxel maintenance therapy to receiving additional treatment cycles. The authors' conclusion was that 12 cycles of single-agent paclitaxel administered to women with advanced EOC who obtained a clinically-defined complete response to initial platinum/paclitaxel-based chemotherapy significantly prolonged the duration of PFS.[51, 85] A follow up publication in 2009 evaluated the impact of extended paclitaxel maintenance on OS. The median OS for the 12-cycle arm versus the three-cycle arm was 53 versus 48 months respectively.[51] This difference was not statistically significant. Crossover of patients from the three-cycle to the 12-cycle arm may have confounded the ability to detect a statistically significant difference. In order to further evaluate the OS question and respond to criticisms of the lack of a pure control arm, the GOG opened protocol 212, randomizing a similar population of patients with complete response to observation versus 12 cycles of paclitaxel (135 mg/m2 every 28 days) maintenance therapy versus 12 cycles of a novel paclitaxel poliglumex (Xyotax™). The primary endpoint of this trial was OS in an attempt to determine if timing of prolonged taxane-based maintenance therapy is critical.[86] With a median follow-up of 8.1 years, median survival durations were 58.3, 56.8, and 60.0 months for observation, paclitaxel, and paclitaxel poliglumex, respectively. There was no difference in OS between each of the arms (compared to observation, the hazard of death for paclitaxel was 1.091 [P=0.343] and for paclitaxel poliglumex, it was 1.033 [P= 0.725]). There was an improvement in PFS in the paclitaxel arm (median of 13.4, 18.9, and 16.3 months for observation, paclitaxel, and paclitaxel poliglumex, respectively. HR= 0.801; 95% CI, 0.684 to 0.938; P=0.006 for paclitaxel and HR = 0.854; 95% CI, 0.729 to 1.00; P=0.055 for paclitaxel poliglumex). The authors discussed the controversy of using OS rather than PFS, as this maintenance therapy failed to demonstrate an OS benefit; however, PFS was superior for patients who received paclitaxel. Both taxanes resulted in significantly worse adverse side effects, especially sensory neuropathy (paclitaxel poliglumex: 10.0%, paclitaxel: 5.4%, observation: 0.8%; P<0.001). In context of the ongoing trials exploring alternate maintenance treatment strategies, the utilization of taxanes as a maintenance approach has been abandoned.

GOG 218 was the first prospective, randomized clinical trial in advanced EOC within the GOG to utilize a targeted agent both with and to follow chemotherapy as maintenance. Based upon the evidence that vascular endothelial growth factor (VEGF) and angiogenesis are important promoters of EOC progression, the design of this study was to evaluate the addition of bevacizumab, a VEGF inhibitor, to standard front line therapy. This trial randomized patients to paclitaxel (175 mg/m2) and carboplatin (AUC 6) chemotherapy for six cycles plus one of the following three targeted agent schedules for a total of 22 cycles: placebo for cycles 2-22 (control), bevacizumab for cycles 2-6 followed by placebo for cycles 7-22 (bevacizumab initiation) and bevacizumab for cycles 2-22 (bevacizumab throughout). The median PFS for the arms were 10.3, 11.2 and 14.1 months respectively with the bevacizumab throughout demonstrating a statistically significant improvement in PFS compared to the control arm .19 With median follow up of 102.9 months, there was no difference in median OS with a HR of death 1.06 (95% CI 0.94-1.20) for bevacizumab concurrent with chemotherapy only (no maintenance) as compared to control and a HR of 0.96 (95% CI 0.85-1.09) for bevacizumab throughout as compared to control. [1]

Based on data from the Japanese Gynecologic Oncology Group20 (JGOG3016) demonstrating a statistically significant improvement in PFS with the use of dose dense paclitaxel in front line EOC, GOG 262 was developed to confirm these findings. This trial randomized patients with initially suboptimally debulked EOC but ultimately opened to include patients with both optimally and suboptimally debulked EOC after the closure of GOG 252 to carboplatin (AUC 6) plus either weekly paclitaxel (80 mg/m2) or every three week paclitaxel (175 mg/ m2). This trial design also allowed for the use of bevacizumab (15 mg/kg every three weeks until progression) at the discretion of the treating physician and patient, selected before randomization. A unique amendment in this trial's design ultimately permitted the use of a neoadjuvant treatment strategy with interval cytoreductive surgery. This trial enrolled 692 patients from 2010 to 2012, 84% of whom opted for treatment with bevacizumab. In the intention to treat (IIT) analysis, there was no difference in median PFS for weekly paclitaxel as compared to every 21 day dosing (14.7 months versus 14.0 months respectively, HR 0.89; 95% CI 0.74-1.016; p=0.18). Among the subgroup of patients who did not opt for bevacizumab, there was a

signal for increased efficacy with weekly paclitaxel (14.2 vs 10.3 months; HR 0.62; 95% CI 0.4-0.95; p=0.03).[2] While hypothesis generating, the results of this study dampened enthusiasm for a weekly approach.

Advanced Stage, Intraperitoneal Chemotherapy

The GOG has been a leader in the development and evaluation of IP chemotherapy in ovarian cancer. The first phase III study demonstrating the superiority of IP chemotherapy for advanced, optimally cytoreduced EOC was a cooperative intergroup study initiated by the Southwestern Oncology Group (SWOG) in 1985 (SWOG 8501). This study compared intravenous (IV) cisplatin and cyclophosphamide to IP cisplatin and intravenous cyclophosphamide. Due to slow accrual, SWOG asked the GOG to join the trial in 1988, and this trial was opened within the GOG as GOG 104 .Eligibility to this trial included all patients with stage III EOC with no residual lesion measuring > 2 cm diameter.[21]

The IP arm was associated with a statistically significant prolongation of survival. The median OS of the IP arm was 49 months compared to 41 months for the IV arm, with a hazard ratio of 0.77. [21]

The study had potential weaknesses, with crtiticism that the treatment arsm were not reflective of contemporary regimens. Paclitaxel, a standard drug in the treatment of newly diagnosed, advanced stage EOC, was not utilized, raising the question as to whether the addition of paclitaxel would potentially neutralize the apparent advantage of the IP administration. Since the control arm did not contain paclitaxel, it was suggested that the study lacked relevance to contemporary treatment planning. With GOG #104 demonstrating an improvement in median OS for the IP arm of the study, the GOG opted to develop a follow-up trial.

GOG 114 compared IV cisplatin (75mg/m2) plus IV paclitaxel (135 mg/m2) over 24 hours for six cycles versus carboplatin (AUC 9) IV every 28 days for two cycles followed by cisplatin (100 mg/m2) IP and paclitaxel (135 mg/m2) over 24 hours IV for six cycles.[22] The study was limited to patients who had stage III disease with < 1 cm of residual tumor following surgery. Between 1992 and 1995, the GOG enrolled 462 patients on this protocol. The median duration of survival for the experimental regimen containing IP cisplatin was 67 months versus 51 months for the IV arm. The treatment hazard ratio for progression-free survival in the IP group was 0.78. Though the study was statistically significant from a PFS standpoint, questions were raised regarding which component of therapy was most important in improving survival. The patients in the experimental arm did receive two cycles of high-dose carboplatin, at an AUC of 9, in addition to the 6 cycles of IP cisplatin.[22]

Further evaluation of intraperitoneal chemotherapy was undertaken in GOG #172, comparing IV paclitaxel (135 mg/m2) over 24 hours with IV cisplatin (75 mg/m2) on day 2 versus IV paclitaxel (135 mg/m2) over 24 hours followed by cisplatin (100mg/m2) IP on day 2 and paclitaxel (60mg/m2) IP on day 8.[23] Treatment in both arms was administered every three weeks for a total of six courses and quality of life was assessed at four time points. As in GOG 114, the patients had optimally surgically resected EOC with residual disease <1 cm after initial surgery. Between 1998 and 2001, a total of 415 eligible patients were entered. Both PFS and OS was significantly improved in the IP arm.[23]

The median OS for the IV and the IP arms was 49.5 and 66.9 months, respectively. The relative risk of death was 0.71 with a 95% confidence interval of 0.54 to 0.94 for the IP group with a P = 0.0076. In spite of this impressive improvement in survival, concern was raised regarding the tolerability of the experimental regimen. Grade 3 and 4 hematologic, metabolic and GI toxicities, as well as fatigue, infection and pain, were significantly more common (p<0.001) on the IP arm. Indeed, only 42% of the patients were able to complete all six cycles of the IP therapy. The authors concluded that compared with standard IV paclitaxel plus cisplatin, an intensive regimen of IV paclitaxel plus sequential IP cisplatin and paclitaxel significantly improved PFS and OS in patients with optimally-debulked stage III EOC.[23] However, the IP regimen used in GOG 172 had substantial toxicity that compromised treatment delivery. [23]

In an effort to improve the tolerability of IP chemotherapy and to further investigate the role of IP chemotherapy relative to dose dense IV chemotherapy, GOG 252 was initiated. The trial enrolled 1560 patients from 2009 to 2011 with optimally debulked EOC although the trial did allow the inclusion of suboptimally debulked patients (N=178) for a portion of the enrollment period after GOG #262 completed enrollment. This trial randomized patients to three arms. The first arm was a modification of the IP arm in GOG #172, reducing the IP cisplatin to a dose of 75 mg/m2 on day 2 for six cycles. The other two arms utilized weekly paclitaxel (80 mg/ m2) IV with either IV or IP carboplatin (AUC 6) for six cycles. All arms included bevacizumab (15 mg/kg) IV every 3 weeks for 21 cycles (cycles 2-22) The statistical rationale of this trial allowed for two comparisons. The first was to compare an IP carboplatin based regimen to the modified GOG 172 IP regimen in

the hopes of reducing toxicity, and the other a comparison of IP to IV carboplatin in addition to dose dense weekly paclitaxel.[3,87]

There was no statistically significant difference in PFS between the IV regimen and either of the IP regimens (compared with IV carboplatin, HR = 0.925 (95% CI, 0.802 to 1.07) for the IP carboplatin arm; HR= 0.977 (95% CI; 0.847 to 1.13) for the IP cisplatin arm; median PFS 24.9 months in the IV carboplatin arm, 27.4 months in the IP carboplatin arm, and 26.2 months in the IP cisplatin arm. There was no statistically significant difference in PFS between the IV regimen and either of the IP regimens (relative to the IV carboplatin group, HR=0.949 (95% CI, 0.799 to 1.128) and IP cisplatin arm (HR=1.05 (95% CI, 0.884 to 1.24). The authors concluded the duration of PFS was not significantly increased with either IP regimen when combined with bevacizumab and was better tolerated than IP cisplatin. The findings of GOG 252 catalyzed the gradual abandonment of IP chemotherapy in the treatment of EOC by many gynecologic oncologists. Currently there are no phase III trials evaluating or utilizing IP chemotherapy in the first line setting.

The publication of GOG 2184 almost a decade ago heralded the end of clinical trials in front line ovarian cancer devoid of biomarker selection or stratification, with BRCA and homologous recombination deficiency (HRD) emerging as validated biomarkers for treatment selection based on GOG Foundation studies.

Based on SEER data between 2001 and 2017, there are reasons to be hopeful for outcomes among women impacted by epithelial ovarian cancer (EOC). Incidence has decreased by 30%, mortality has decreased by 27% and the prevalence of women living with EOC has increased by 39%.5 While the reasons behind these positive changes are not entirely known, the identification and availability of novel and effective treatment options has certainly played a role, with 12 new drug approvals since 2014 including bevacizumab[6], olaparib[7], rucaparib[8], niraparib[9] and pembrolizumab for microsatellite instable high (MSI-H) tumors.[10] The continued development and access to novel therapies, surgical interventions, enhanced identification of genetic biomarkers, and better supportive care have contributed to the current improved state of ovarian cancer survivorship.

GOG Foundation Studies in the Front Line Treatment of Ovarian Cancer: Post GOG 218 accomplishments

The typical course of epithelial ovarian cancer (EOC) is well understood. The majority of women present with advanced stage disease, are exquisitely sensitive to initial front line platinum based therapy, although unfortunately, over 75% will recur within three years of completing therapy. Once recurrent, there are many options to effectively treat EOC which meaningfully prolong life, but cure is no longer expected, generally the result of accelerating treatment resistance. [11,12] The concept of maintenance therapy evolved due to the high proportion of women who are not cured with front line therapy, despite what appeared to be a complete response to treatment. As discussed earlier, the incorporation of bevacizumab both concurrent with and to follow completion of chemotherapy for 18-22 cycles was evaluated in the GOG protocol 218 and ICON 7, with both studies reporting similar results with an approximate 20 to 30% reduction in the hazard of progression or death with addition of bevacizumab concurrent with and to follow chemotherapy. [1,4,13] There was no improvement in overall survival (OS) and this led investigators to question whether the bevacizumab had been stopped too early and if longer duration of use would build on the PFS success of the prior studies. In a study performed outside the GOG-F, AGO-OVAR 17/BOOST was developed to determine if 30 vs 15 cycles of bevacizumab following concomitant paclitaxel and carboplatin and bevacizumab would translate into improved outcomes. There was no difference in PFS with a hazard ratio (HR) of 0.9 (0.5-1.15) and median PFS of 24.2 vs. 26 months in the 15 and 30 month arms respectively. Additionally, there was no benefit in OS nor in any clinical risk subgroup.[14] Therefore the standard of care for bevacizumab remains 15 additional cycles as studied in GOG 218. While this improvement in PFS is clinically meaningful, the search for medications such as PARPi which could potentially prevent recurrence or at least result in a more substantial delay in recurrence was needed.

EOC reflected an ideal setting for the examination of PARPi efficacy, in the context of highly prevalent deficiency in double strand DNA repair (homologous recombination deficiency; HRD). HRD is identified in approximately 50% of high grade serous (HGSOC) and high grade endometrioid EOCs.

SOLO-1/GOG 3004 was the first clinical trial to incorporate the PARPi, olaparib into the front-line maintenance treatment paradigm. SOLO-1 enrolled women with BRCA1/2 associated EOC who were in response to combination of surgery and front line platinum based chemotherapy. Women were randomized in a 2:1 fashion to receive olaparib 300mg tablets po twice daily (bid) or placebo until disease progression or toxicity. At two years from randomization, if no progression was noted, women were to be discontinued from assigned therapy. The primary endpoint was PFS as assessed by the investigator. Details about patient demographics are outlined in Table 1. Use

of olaparib led to an unprecedented reduction in the hazard for progression or death (70%) (HR of 0.30 (95% CI 0.23-0.41; p<0.0001). With now 60 months of follow up, the median PFS for placebo was 13.1 months as compared to 56 months for use of olaparib .15,16 Subsequent exploratory analyses evaluated the magnitude of benefit for women who underwent primary versus interval cytoreduction surgery (pCRS vs iCRS). The HR for benefit for women who underwent pCRS was 0.31 (95% CI 0.21-0.46) and for those who underwent iCRS was HR 0.37 (95% CI (0.24-0.58). Similarly, the magnitude of benefit was maintained regardless of the presence of no residual disease (NGR) after surgery (HR 0.33 [95% CI 0.23-0.46]) or residual disease (HR 0.44 (95% CI 0.25-0.77). Even among women with stage III EOC, who underwent pCRS to no gross residual (NGR) the mPFS was 21.9 vs. NR; HR 0.32 (0.20-0.51). This group of women with BRCA associated cancers, even with the best surgical prognostic factors, still recur without maintenance therapy.[17] Among women who entered the study with a complete response, the HR was 0.37 (95% CI 0.27-0.52) with median PFS of 22 vs. 52 months.16 The percentage of women disease free at 5 years was 21% vs. 48% in the placebo vs. olaparib group respectively. At seven years of follow-up, the OS continues to be immature though the impact of olaparib persists with a 45% reduction in the risk of death (HR 0.55 (95% CI 0.40–0.76); P=0.0004; P<0.0001 required to declare statistical significance) with median OS still not reached in the olaparib arm and 75.2 months in the placebo arm. Amazingly, 45.3% of those on olaparib are alive and have not started a subsequent therapy (TFST) at 84 months (seven years) compared to 20.6% of patients on the placebo arm, speaking to the potential for curative intent in patients with advanced stage ovarian cancer.[88] SOLO-1, and all subsequent exploratory analyses completed as part of the trial, emphasize the finding that PARPi mainteinance therapy is the standard of care for women with BRCA associated cancers who are in response to front line therapy irrespective of clinical risk factors.

Following SOLO-1, 4 additional studies were presented all evaluating use of PARPi inclusive of BRCA-associated cancers but also BRCA wild type (wt) with HGSOC +/- endometrioid tumors. Three of these studies were GOG-F studies, PRIMA/ENGOT-OV26/GOG 3012, VELIA/GOG 3005 and ATHENA-MONO/GOG 3020.

PRIMA/ENGOT-OV26/GOG-3012 enrolled women with advanced HGSOC or endometrioid EOC who were stage III with residual disease, stage IV and those treated with neoadjuvant chemotherapy (NACT). Similar to SOLO-1, women had to be in either CR or PR following platinum and taxane-based chemotherapy but unlike SOLO-1, BRCA mutation was not required. Women were randomized in a 2:1 ratio to niraparib once daily or placebo and were treated until disease progression, toxicity or 36 months. The primary endpoint as measured by blinded independent radiographic review was performed as a hierarchal analysis with PFS in HRD tumors first and if significant then in the overall population (ITT). Among women with HRD tumors, the reduction in the hazard for progression or death was 57% (HR of 0.43 [95% CI: 0.31-0.59; p<.001]). The median PFS was 21.9 vs. 10.4 months. In the ITT group, the reduction in the risk of progression or death was 38% (HR of 0.62 (95% CI 0.50-0.76; p<0.001)). The median PFS for the ITT was 13.8 vs. 8.2. In non-hypothesis (non-analytic) tested subgroups, the reduction in the hazard for progression or death are as follows: HRD/BRCA+ HR 0.40 (95% CI 0.27-0.62); HRD/BRCAwt HR 0.50 (95% CI 0.31-0.83) and HRp/HRunknown HR 0.68 (95% CI 0.49-0.94).[18] The subset analyses results for women with BRCA-associated tumors enrolled to PRIMA are consistent with those seen in SOLO-1. It is also important to note that the HR tumor test performed in this analysis was based on algorithmic measure for three tumor factors: loss of heterozygositiy (LOH), telomeric allelic imbalance and large-scale state transitions. For PRIMA, HRD was defined as a score of > 42 OR having a BRCA associated cancer. Niraparib is currently listed as a maintenance option following front line therapy and gained FDA approval for this use on April 29, 2020.[9,19]

The VELIA/GOG 3005 randomized phase III trial is the only front-line study to incorporate a PARPi (veliparib) both during and to follow front line chemotherapy. This study enrolled women at the beginning of chemotherapy (which is distinct from SOLO-1, and PRIMA which enrolled women who had responded to platinum based combination chemotherapy). Eligible women with HGSOC, stage III or IV and good performance status were randomized 1:1:1 to veliparib throughout versus veliparib with chemotherapy followed by placebo vs. placebo throughout. The veliparib dosing with chemotherapy was 150mg po BID. Once maintenance was reached it was increased to 300 mg and then 400 mg po bid by cycle 7. Maintenance cycles were 21 days and continued until disease progression, toxicity or cycle 30. The primary endpoint was PFS as assessed by the investigator in the veliparib throughout compared with the placebo throughout group and analyzed sequentially in women with BRCA associated cancers, then HRD and finally IIT. HRD was measured with the same assay as used in PRIMA and PAOLA, however the cut-off score for HRD was > 33. It is worth reinforcing the differences in VELIA compared to other trials; the mPFS values for VELIA include the time spent on chemotherapy AND include the contribution of

Table 1.

			ORR			
Front Line						
PSOC						
	GOG 146B	Tomudex	SA Ph2			
	GOG 146C	Topotecan	SA Ph2 N=46	32.6% (90% CI 19.5-48)	mPFS 9.6 mo mOS 20.2	No
	GOG 146D	Pyrozolacridine	SA Ph2 N=42	23.8%	NR	No
	GOG 146E	CI-958				
	GOG 146F	24 hr Topotecan				
	GOG 146H	Brostatin				
	GOG 146J	Dolostatin				
	GOG 146L	Capecitabine				
	GOG 146M	Tirpazapine + cisplatin				
	GOG 146K	3 d Topotecan				
	GOG 146N	Bortezomib				
	GOG 146O	Irofulven				
	GOG 146P	Cetuximab and Carboplatin				
	GOG 146Q	Topotecan (2 reg)				
PROC						
	GOG 126B	Cisplatin and Cyclosporin	SA Ph2			
	GOG 126C	Altretamine	SA Ph2			
	GOG 126D	Pyrazoloacridine	SA Ph2			
	GOG 126E	Paclitaxel & Valspodar	SA PH2			
	GOG 126G	C1-958	SA Ph2			
	GOG 126H	24hr Topotecan	SA Ph2			
	GOG 126I	9 aminocamptothecin	SA Ph2			
	GOG 126J	Doctaxel	SA Ph2			
	GOG 126K	Oxaliplatin	SA Ph2			
	GOG 126L	Cisplatin + Gemcitabine	SA Ph2			
	GOG 126M	Ixabepilone	SAPh2			
	GOG 126N	Weekly Paclitaxel	SA Ph2			
	GOG 126O	Ribonucleotide reductase inhibitor	SA Ph2			
	GOG 126Q	Pemetrexed	SA Ph2			
	GOG 126R	Nab-Paclitaxel	SA Ph2			

Table 1. (*cont'd*)

GOG 126T	Belinostat	SA Ph2
GOG 160	Trastuzumab	
GOG 170B	IL-12	
GOG 170C	Gefitinib	
GOG 170D	Bevacizumab	
GOG 170E	Imatinib methylate	
GOG 170F	Sorafenib	
GOG 170G	Lapatinib	
GOG 170H	Vorinostat	
GOG 170I	Temsirolimus	
GOG 170J	Enzastaurin	
GOG 170K	Mifepristone	
GOG 170L	Motesanib (AMG 706)	
GOG 170M	Dasatinib	
GOG 170N	Urokinase derived peptise (A6)	
GOG 170P	Rilotumumab	
GOG 170Q	IP EGEN-001	
GOG 186C	Paclitaxel Poliglumex	
GOG 186D	Karenitecin	
GOG 186F	Docetaxel + Trabectedin	
GOG 186G	Bevacizumab +/- everolimus	RPh2
GOG 186H	Weekly PAC +/- reolysin	RPh2

women who either progressed on chemotherapy or had stable disease and were not eligible for the previously discussed trials. Among women with BRCA associated cancers, the mPFS was 22 vs 34.7 months, (HR of 0.44 [95% CI 0.28-0.68; p<0.001]). In the HRD population the mPFS was 20.5 vs. 31.9 months (HR of 0.57 [95% CI 0.43-0.76; p<0.001]) and in the ITT population, the mPFS was 17.3 vs. 23.5 months (HR of 0.68 [95% CI 0.56-0.83]). In non-hypothesis tested subgroups, the HR are as follows: BRCAwt mPFS 15.1 vs 18.2, (HR 0.80 [95% CI 0.64-0.997]); HRD/BRCAwt mPFS 19.8 vs 22.9, (HR 0.74 [95% CI .52-1.06]) and HRp mPFS 11.5 vs 15, (HR 0.81 [95% CI 0.60-1.090]).[20]

ATHENA-MONO/GOG-3020 enrolled patients with stage III or IV high-grade ovarian cancer. Patients who underwent a complete, R0, resection were permitted to enroll on trial. Analagous to SOLO-1 and PRIMA, patients who responded to first-line platinum-doublet chemotherapy were randomly assigned 4:1 to oral rucaparib 600 mg twice a day or placebo. The primary end point of investigator-assessed progression-free survival was assessed in a step-down procedure, first in the HRD population (BRCA-mutant or BRCA wild-type/loss of heterozygosity high tumor), and then in the intent-to-treat population. Unlike the other trials, HRD tumor testing was performed using the FoundationOne CDx next-generation sequencing assay, with HRD test positive defined as an LOH score ≥16%. The benefit of rucaparib therapy was seen with respect to investigator-assessed PFS in the HRD population, with median PFS of 28.7 months (95% CI, 23.0 to NR) in the rucaparib group versus 11.3 months (95% CI, 9.1 to 22.1) in the placebo group (HR=0.47; 95% CI, 0.31 to 0.72; log-rank P=0.0004); In the intention to treat population,

median PFS was 20.2 months (95% CI, 15.2 to 24.7) in the rucaparib group versus 9.2 months (95% CI, 8.3 to 12.2) in the placebo group (HR= 0.52; 95% CI, 0.40 to 0.68; log-rank P<0 .0001). Exploratory subgroup analyses of investigator-assessed PFS in the ITT population showed that there was greater clinical benefit with rucaparib versus placebo for all subgroups by investigator assessed PFS: BRCA-mutant (HR= 0.40; 95% CI, 0.21 to 0.75; PFS: NR (25.8 to NR, 95% CI) versus 14.7 m (6.4 to NR, 95% CI); BRCA wild-type/LOH high (HR, 0.58; 95% CI, 0.33 to 1.01; PFS 20.m (13.4 to 31.1, 95% CI versus 9.2 m (4.0 to 22.1m, 95% CI); BRCA wild-type/LOH low (HR, 0.65; 95% CI, 0.45 to 0.95; PFS 12.1m (11.1 to 17.7, 95% CI) versus 9.1m (4.0 to 12.2, 95% CI).[89]

Given the results of these trials, PARPi use has been incorporated into the treatment paradigm for front line ovarian cancer. Based on the magnitude of benefit, use of maintenance PARPi should be considered the standard of care (allowing for obvious contraindications) in the front-line treatment of women with BRCAmut and HRD associated cancers. For those women with HRp tumors, niraparib and rucaparib are options, with reasonable clinical benefit, but clinical equipoise remains and better therapies are needed refelcting an active area of investigation.

In an effort to improve front-line outcomes and build upon the success of bevacizumab, the GOG 3015/ENGOT OV39 (IMagyn050) study was launched to evaluate the potential benefit of the anti PD-L1 monoclonal antibody atezolizumab in combination with bevacizumab with and to follow chemotherapy. Incorporation of bevacizumab with and to follow front line paclitaxel and carboplatin chemotherapy is a standard of care in many parts of the world with significant improvements in PFS as mentioned previously (GOG 218). In addition to the anti-angiogenic effect, blocking VEGF has been shown to increase cytotoxic T cell trafficking into many solid tumor types, justifying combinations with anti-PD1 and PD-L1 monoclonal antibodies. The pronounced anti-tumor effects of combining anti-angiogenics and anti-PD1/PD-L1 therapies have been demonstrated in metastatic NSCLC, HCC and endometrial cancer.

To determine if this this benefit extended into EOC, IMagyn050 tested the hypothesis that incorporating the anti-PDL1 agent (Atezolizumab) into a Bevacizumab-containing frontline chemotherapy regimen would impart clinical efficacy with acceptable safety. This randomized phase III study enrolled treatment naïve patients with advanced EOC and randomized 1:1 to paclitaxel/carboplatin/bevacizumab + Placebo x six cycles followed by bevacizumab/placebo x 16 additional cycles or paclitaxel/carboplatin/bevacizumab/Atezolizumab x 6 followed by 16 cycles of bevacizumab/atezolizumab. Randomization was stratified by stage, PS, timing of surgery and PD-L1 status as measured by the SP142 assay. The co-primary endpoints were PFS tested simultaneously in both the PD-L1+ and ITT populations as well as OS with hierarchical testing – PD-L1+ then ITT. The proportion of patients scheduled for NACT was limited to 20%. The baseline characteristics for the ITT population included, 25% received NACT, 60% had PD-L1+ tumors, 31% had stage IV disease, and approximately 75% had tumors with HGS histology.

Unfortunately, adding Atezolizumab to the chemotherapy plus bevacizumab backbone resulted in a non-significant 1.1 month prolongation in PFS in the ITT population (HR 0.93; 95% CI 0.79 -1.07; p=0.2785). In the fully powered PD-L1 positive population, adding Atezolizumab also only resulted in a non-significant 2.3 month numeric increase in PFS (HR 0.80; 95% CI 0.65-0.99 p= 0.0376). Exploratory analyses revealed interesting subgroups such as the very small group of tumors characterized as clear cell (n=51) who had a 36% reduction in the hazard of progression or death with addition of atezolizumab (HR 0.64; 95% CI 0.33-1.24) but this was a small patient sample and not hypothesis tested. Similarly, subgroup analysis by PD-L1positivity found that those tumors with 5% or higher PD-L1 positivity (20% of the population) seemed to benefit from addition of atezolizumab as well (HR 0.64; 95% CI 0.43-0.96). Again, the value of this exploratory data is to inform future study hypothesis in an effort to identify effective immunotherapeutic approaches in the ovarian cancer space. Further evaluation found no association between BRCA or HRD status and response to atezolizumab.[21]

At this point, there is no indication for use of immune checkpoint inhibitors in the front line setting for the management of ovarian cancer, although several ongoing, GOG-F led studies may identify patients who will benefit for multi-pathway therapy.Additionally there are two trials that are deisgned to examine if additional immune therapies, alternative pathway inhibition/targeting or hyperthermic intra-peritoneal chemotherapy at the time of surgical resection may be of therapeutic benefit, especially in the high unmet need of patients found to be HRD test negative (HRp).

Secondary Cytoreduction: GOG 213 and DESKTOP

In patients with PSOC, the utility of additional surgical intervention has been debated, and incorporated into clinical practice. Multiple retrospective cohort studies have shown increased survival if CRS to no gross residual

(NGR) is achieved. [22-25] Similar to the upfront setting, identifying patients who are amenable to complete surgical cytoreduction is not straightforward and the lack of consistent and validated selection criteria may have contributed to the opposite results of two large randomized phase III studies (RPh3) evaluating the role of surgery in this setting. These two trials are GOG protocol 213 and DESKTOP OVAR III (Descriptive evaluation of Preoperative Selection Kirteria for Operability in Recurrent Ovarian Cancer). In the DESKTOP OVAR trial, 267 patients were randomized to secondary CRS or not – each arm subsequently treated with platinum based chemotherapy. Patients were eligible for this trial given that they met AGO criteria which were developed in the DESKTOP II trial and included: 1) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to; 2) ascites < 500 cc; and 3) no residual tumor at their initial primary CRS. DESKTOP II prospectively validated the score used in DESKTOP OVAR and predicted complete resection in 75% of patients who were score "positive." [23,26] The primary endpoint for DESKTOP OVAR III was overall survival (OS) which was met with a median of 53.7 months vs. 46.0 months (hazard ratio (HR) 0.75; 95% CI 0.58-0.96; p=0.02). The benefit among patients with CRS to NGR was 61.9 vs. 46.0 months (HR 0.57; 95% CI: 0.43-0.76). Two additional important points from this RPh3 study; first the AGO score developed and validated in this series of trials, selects out 50% of "platinum sensitive patients" for this intervention and second, among patients were we "pick wrong" – i.e. – go to the operating room and fail to achieve NGR, the oncologic outcome is worse than had they had no attempt at surgery at all with a median PFS of 28.8 vs. 61.9 (gross residual vs. NGR) (HR 0.40 (95% CI 0.28-0.59; p<0.001)). This emphasizes the importance of appropriate patient selection if secondary surgical cytoreduction is being considered in the PSOC setting. [27]

This lack of pre-specificied patient selection criteria as well as alternate study specific factors may explain the different results seen in GOG 213. This study had two primary objectives.[28] The first assessed the impact of bevacizumab administered concomitantly with paclitaxel and carboplatin as well as in maintenance on OS (primary endpoint). The second evaluated the impact of secondary CRS (versus no surgery) on OS. Determination of who was eligible for surgery was at the discretion of the treating physician with some requirements such as complete response (CR) to front line chemotherapy, no evidence of bowel obstruction or need for parenteral nutrition and no evidence of carcinomatosis or parenchymal organ disease that was felt to be unresectable. Complete resection was achieved in 67% of patients. Despite this high level of CR, OS was negatively impacted by secondary CRS with a median of 53.6 vs. 65.7 months, (HR 1.28;(95% CI 0.92-1.78; p=0.08) in favor of no surgery. 29 Why these significant differences exist between these two trials remains speculative. The differing eligibility may be relevant, although the use of bevacizumab in GOG 213, which may have blunted any obvious impact of surgery on OS, is also an important consideration. An important, and unfixable issue, is that the outcomes of women with PSOC have (fortunately) improved since the original design and enrollment of GOG 213 which occurred almost a decade prior to results. The final OS is three times as long as what was predicted when the study was designed. The emergence of effective post progression treatments and the incredible lengthening of OS may have masked any benefits seen with secondary surgery.[29] There is one additional RPh3 study, SOC-1 for which OS is still pending. This trial enrolled 356 patients and eligibility was based on a clinical score (TIAN score) plus findings on PET/CT imaging. Thus far only progression free survival has been presented – favoring secondary CRS with a HR of 0.58; p < 0.001, although OS is the primary endpoint.30 Currently, secondary CRS is a reasonable consideration in appropriately selected platinum sensitive recurrent ovarian cancer patients, understanding that future trial results may further inform this approach.

Platinum Sensitive

There are essentially two broad concepts of maintenance therapy: secondary maintenance and switch maintenance. Studies that are evaluating secondary maintenance are generally designed as a treatment combination, commonly chemotherapy and a biologic, where one or more agents, but not the induction regimen, is continued until progression or some defined duration of therapy.[28,31,32] In contrast, switch maintenance therapy involves a therapy that is new to the treatment plan following a desired response to induction therapy.

The relationship between factors driving the development of tumor-associated vasculature and outcomes in EOC has been well documented.[33-47] The monoclonal antibody targeting vascular endothelial growth factor, bevacizumab, has been most widely studied in a secondary maintenance strategy. Phase III trials assessing bevacizumab in this setting were OCEANS and GOG-0213. Besides assessing the role of surgical CRS as discussed above, GOG-0213 examined the impact of bevacizumab administered concomitantly with paclitaxel and carboplatin as well as in maintenance on OS (primary endpoint) among patients with one prior line of treatment. Bevacizumab administered concomitantly with chemotherapy and in maintenance improved OS relative to chemotherapy alone (median 42.2 vs 37.3 months, adjusted HR:

0.823, 95% CI: 0.68 - 0.996, P=0.045). Similar to OCEANS, GOG-0213 significantly improved PFS (median: 13.8 vs. 10.4 months, HR: 0.63, 95%CI: 0.53-0.74, P<0.0001), as well as ORR (78% vs 59%, P<0.0001), including a near doubling of the CR rate (32% vs 18%). On the basis of OCEANS and GOG-0213, the U.S. FDA approved bevacizumab in combination with chemotherapy for patients with PSR EOC in 2016.[6]

PARPi Maintenance following Response to Platinum in the Recurrent Setting

The initial approvals for PARPi maintenance therapy in EOC were based on randomized trials in the platinum sensitive recurrent setting and are largely biomarker independent. These non-GOG Foundation trials led to approvals for olaparib, niraparib and rucaparib in the platinum sensitive maintenance setting. [7, 9, 48, 55]

Since the original indications, the approval of rucaparib and niraparib in non-BRCAmut patients has been withdrawn. These four trials established a new standard of care for women with platinum sensitive recurrence who have response to platinum-based therapy, although this paradigm is now being questioned. All of these trials were performed in patients who were naïve to prior PARPi exposure. The challenge before providers now and in the future is what to do for a non-BRCA patient who has not previously received a PARPi and who has a marked clinical response to platinum. Furthermore, the appropriate management of a patient that has previously been treated with a PARPi for front line maintenance therapy, and who did not progress on a PARPi remains unknown. The OREO/ENGOT ov-38 phase III trial of olaparib maintenance re-treatment in patients with epithelial ovarian cancer (NCT03106987) showed a modest, though statistically significant, improvement in median PFS 5.3 versus 2.8 m (HR 0.43 [95% CI 0.26–0.71]; P=0.0023) though the impact of these results on the ovarian cancer lansdscape remains unknown.[90]

Non-chemotherapy options with PARPi The efficacy of PARPi as monotherapy in biomarker selected populations has been demonstrated in three, single arm phase II trials. The initial study of olaparib is the first study to lead to accelerated approval of a PARPi by the FDA on December 19, 2014.[7] This trial, known as Study 42 was a basket trial which included BRCA-associated EOC. In this population of patients who were either classified as resistant to or inappropriate for further platinum and who had >3 lines of chemotherapy, olaparib resulted in an ORR of 31% (95% CI 24.6 to 38.1) and a DOR of approximately eight months.[7,56] The second, similar data set came from combination analysis of ARIEL2 and Study 10. Including just those patients who had either a germline or somatic BRCA mutation and had received >2 lines of chemotherapy, the studies found an ORR of 54% (44% - 64%) and median DOR of 9.2 mos (6.6 - 11.6). This resulted in FDA approval for rucaparib in germline or somatic BRCA-associated cancers with >2 prior lines of therapy.[8,57-58] Niraparib was approved for patients with platinum sensitive, HRD recurrent EOC who had received >3 prior lines of chemotherapy.[9] This was based on the QUADRA study which was a phase II, single arm study evaluating niraparib in patients with recurrent EOC who received > 3 prior chemotherapy regimens. The primary endpoint for this study was overall response rate (ORR) among platinum sensitive, recurrent tumors who were HRD. ORR in the primary efficacy population was 27.7% (95% CI 15·6–42·6 and mOS was 17.2 months.[59] Importantly, all of these treatment approvals have been voluntarily withdrawn given concern about implications of exposure on overall survival.

While demonstrating the potential efficacy of monotherapy PARPi , none of these studies confirmed that PARPi is superior or even equivalent to other standard medicines. The GOG Foundation led one of the first studies comparing a non-platinum containing therapy to PARPi and PARPi combination therapy in the platinum sensitive setting. NRG-GY004 (NCT02446600) is a phase III study comparing single agent olaparib or the combination of cediranib and olaparib to standard platinum-based chemotherapy in patients with recurrent platinum sensitive EOC. Patients included in the study received < 3 prior lines of chemotherapy, had measurable disease, and were PARPi naive. Median PFS was 10.3 (95% CI, 8.7 to 11.2), 8.2 (95% CI, 6.6 to 8.7), and 10.4 (95% CI, 8.5 to 12.5) months with chemotherapy, olaparib, and olaparib plus cediranib, respectively. Olaparib plus cediranib did not improve PFS versus chemotherapy (hazard ratio [HR] 0.86; 95% CI, 0.66 to 1.10; P = .077). In women with germline BRCA mutation, the PFS HR versus chemotherapy was 0.55 (95% CI, 0.32 to 0.94) for olaparib plus cediranib and 0.63 (95% CI, 0.37 to 1.07) for olaparib alone. In women without a germline BRCA mutation, the PFS HR versus chemotherapy was 0.97 (95% CI, 0.73 to 1.30) for olaparib plus cediranib and 1.41 (95% CI, 1.07 to 1.86) for olaparib. In 489 patients evaluable for PROs, patients receiving olaparib plus cediranib scored on average 1.1 points worse on the NFOSI-DRS-P subscale (97.5% CI, -2.0 to -0.2, P = .0063) versus chemotherapy.60 The use of PARPi in the first line maintenance, the withdrawal of the other PARPi indications in the PSOC setting, the detrminent on PRO and the lack of maintenance therapy included in the control arm brings into question the applicability of this study's findings.

NRG-GY005 (NCT02502266) is a randomized phase II/III study of the combination of cediranib and olaparib compared to cediranib or olaparib monotherapy, or standard of care non-platinum chemotherapy in patients with recurrent platinum resistant EOC. The phase II portion of the trial completed accrual and the independent data monitoring committee (IDMC) reviewed outcomes and elected to re-open the phase III portion of the trial without the option to randomize to single agent olaparib. The phase III portion of the has completed accrual and results are maturing.[61]

PARPi Combinations/Immunotherapy

PARPi have been found to upregulate PD-L1, to upregulate stimulator of interferon gene (STING) [62] and enhance immune cell infiltration into tumors which provides a rationale for the combination of PARPi and immune-oncology agents. [63] Despite this compelling rationale, results of this combination thus far have been modest.

TOPACIO evaluated pembrolizumab and niraparib in patients with recurrent, platinum resistant EOC. Notably, 73% of participants were BRCAwt. Confirmed ORR was 18% and did not vary by BRCA or HRD status. Median duration of response was not reached.[64,65] A phase 2 study of durvalumab (anti PD-L1) monoclonal antibody) and olaparib was conducted in 35 patients, 17% with BRCA associated EOC. The ORR was 15% with 2/5 partial responses occurring in patients with a BRCA associated cancers. (NCT02484404)[66] GOG-F lead GOG 3032, the Moonstone study, which evaluated combination dostarlimab and niraparib in platinum resistant cancers without a BRCA mutation. (NCT03955471). Unfortunately the study findings were negative with a ORR of 7.3% in 41 patients. Exploratory analysis suggested that CPS score (5%) was not predictive of benefit.

Platinum Resistant

GOG 3011 FORWARD-1: The GOG-F led the first study of an antibody drug conjugate (ADC) in platinum resistant ovarian cancer. Mirvetuximab soravtansine is an ADC that targets folate reception α (FRα) and is conjugated to a maytansinoid DM4 which is a highly potent microtubule toxin. Patients were selected based on FRα expression (medium or high), 1-3 priors and having platinum resistant disease and were randomized 2:1 to mirvetuximab versus investigator choice chemotherapy (topotecan, weekly paclitaxel or pegylated liposomal doxorubicin) with PFS as an endpoint in both the ITT and FRα high cohorts. While benefit was seen in the primary and secondary endpoints in the FRα high subgroup, none reached the predefined statistical benchmarks for significance. For the primary endpoint of PFS, the PFS was longer in the mirvetuximab group compared with the investigator choice (median 4.8 months versus 3.3 months; HR 0.69: 95% CI 0.48-1.00; p=0.049).[67] On post hoc exploration as to why this study failed, it was discovered that the scoring for the FRα assay was performed erroneously allowing 30% of the participants to enter the study with FRα low status (ineligible) and further, 50% of the patients designated as FRα high were actually FRα medium on re-analysis. Therefore, the scoring for the FRα assay was re-assessed and the study was redesigned with updated statistics and eligibility for just FRα high as GOG 3045 (MIRASOL: NCT04209855) which is enrolling at the time of this report.

NRG GY003: NRG GY003 studied a broader population than the typical platinum resistant population in that it included women whose tumors had progressed < 12 months from their last carboplatin. This randomized phase 2 study compared nivolumab every two weeks versus induction ipilimumab for four doses followed by every two-week nivolumab with an endpoint of overall response rate (ORR) within the first six months of dosing. This study enrolled 106 patients and ORR was significantly higher in the combination arm at 31.4% versus 12.2%. (odds ratio 3.28; 85% CI 1.54-infinity; p=0.034). The median PFS in each group was 3.9 and 2 months respectively (HR 0.53; 95% CI 0.34-0.82). While a significant improvement in ORR was noted, the median PFS was somewhat disappointing as was the median duration of response of 6 months or more which occurred in 15.7 and 8.2% respectively.[68]

A number of trials have completed enrollment or are currently enrolling, looking to identify novel treatment strategis in the PROC space. Broadly these trials are grouped with agents that combine with weekly taxanes, ADCs, immune therapy or agents that target the DDR pathway.

Rare Tumors

Low Grade Serous EOC: Early studies within the GOG included low grade serous cancers along with all other histologies in clinical trials. With increased understanding of the differences in molecular origin and clinical behavior, these rare tumors have been carved out into their own study series with improved outcomes. GOG 239 was the first attempt to study these unique tumors with a targeted therapy – selumetinib. The MEK inhibitor was selected based on the understanding that LGSOC is a RAS driven tumor where targeting the MAPK pathway may be beneficial. Farley et al. enrolled 52 women with recurrent LGSOC and reported an ORR of 15% with no association with BRAF or KRAS mutations.[69,91]

GOG 281: The above findings led to the development of a randomized phase 3 trial comparing the MEK inhibitor trametinib versus investigator choice therapy (including letrozole) with PFS as an endpoint for LGSOC. This study enrolled 260 patients with recurrent disease. The median PFS was 13.0 vs. 7.2 months (HR 0.48; 95% CI 0.36-0.64; p<0.0001). The ORR was 26.2% for trametinib versus 6.2% for investigator choice therapy. (Odds ratio 5.4; 95% CI 2.39-12.21; p<0.0001).[70]

NRG GY019: The GOG Foundation is now running the first, randomized phase 3 trial aimed at improving outcomes in the front line for women with advanced LGSOC. This study, NRG GY019 randomizes women with Stage II-IV LGSOC to either paclitaxel and carboplatin x 6 followed by letrozole maintenance until progression or toxicity as compared to letrozole 2.5 mg orally continuous until progression or toxicity. The endpoint for this trial is PFS and the trial is currently accruing patients at the time of this report.

GOG 3052: The GOG foundation is also proud to partner with Verastem to bring the RAMP trial (NCT04625270) to the recurrent LGSOC setting. This trial evaluates the dual MEK/RAF inhibitor VS-6766 with or without the addition of a FAK inhibitor in a study stratified by KRAS mutation status. Combination of MEK and RAF inhibition prohibits the phosphorylation of MEK that occurs with a MEK inhibitor alone and leads to resistance. In addition, inhibition of MEK leads to upregulation of FAK which is leads to increased tumorigenesis. This study is accruing at the time of this report.

Malignant Germ Cell

The early experience of the GOG in the treatment of malignant germ cell tumors of the ovary was presented in two publications: a preliminary report in 1978 and a final report in 1985.[36, 37] Protocols GOG 10 and GOG 11 were opened in 1971 to study the effect of multi-agent chemotherapy on malignant germ cell tumors since prior reports had failed to demonstrate success with surgery alone or surgery combined with irradiation or single agent chemotherapy. During the first year, three-drug combinations using dactinomycin, 5-flurouracil, cytoxan and methotrexate were tried, but from 1972 until the phase II study closed in 1978, the regimen of therapy was vincristine, dactinomycin and cyclophosphamide (VAC). In the 1978 preliminary report, there were 27 patients with endodermal sinus tumor, embryonal carcinoma and mixed tumors. Stages var ied from IA through III and four patients had recurrent disease.[36] There were 12 patients with immature teratoma stages IA through III with two patients having recurrent disease. For the endodermal sinus tumor group, 16 of 27 patients (58%) who received VAC were alive and well. For those patients with resection of all gross tumors, 11 of 16 patients (69%) were alive and well. Of patients with advanced/recurrent disease, 45% remained disease free. For the immature teratoma patients, all completely resected patients (8) were living following chemotherapy, although one required a second operation to excise residual grade 1 teratoma. Only one of the four patients with unresected disease was disease-free following chemotherapy and three operations to resect disease.36 The final report in 1985 reported 76 patients with malignant germ cell tumors treated with postoperative VAC. Only 15 of 54 tumors (28%) failed following complete resection of disease followed by VAC chemotherapy. VAC chemotherapy, however, was only ef fective in about 32% of incompletely resected patients and, again, this was true of all cell types.[37]

These early GOG studies of malignant germ cell tumors demonstrated the importance of complete tumor resection and the value of combination chemotherapy with VAC. They also demonstrated the importance of histology as the overall failure rate for endodermal sinus tumors was 48%, and for mixed germ cell tumors it was 53%, while only 18% of grade 2 and 3 immature teratoma tumors failed.[36, 37]

Between 1978 and 1987, the GOG evaluated adjuvant vincristine, dactinomycin and cyclophosphamice (VAC) in malignant germ cell tumors of the ovary after resection of all gross tumors (phase II) and vinblastine, bleomycin and cis-platinum (BVP) in stage III and IV and recurrent malignant germ cell tumors of the ovary.[38- 40] An abstract was presented at the Society of Gynecologic On cologists annual meeting in February, 1989, described 126 evaluable patients stages I, II, and III with thorough surgical stag ing and complete tumor resection.38 One hundred patients received six to nine courses of VAC. At the time of presentation, with a me dian follow-up of four years, 78% of the patients were disease- free. The disease-free rate for endodermal sinus tumors was 73% (35 of 48 patients) and, for grade 2 and 3 immature teratomas, the disease-free rate was 84% (42 of 50 patients). The authors also reported on 26 patients who were treated with three courses of BVP over nine weeks. Twenty-four of 26 of these patients (92%) had median follow-up of 19.2 months. Nine of 10 patients with mixed germ cell tumors were disease-free; and nine of nine patients with endodermal sinus tumors and six of seven patients with immature teratoma were disease-free as well. They stated that although fol low-up was short, they believed the BVP regimen to be superior.[38]

Also in 1989, investigators from the GOG reported on 97 evaluable patients with stage II through IV and recurrent malignant germ cell tumors treated with BVP.39 Five patients were stage II; 37 were stage III; nine were stage IV; and 38 patients had recurrent disease. Thirty-seven percent of the non-dysgerminoma patients were recurrent after VAC chemotherapy. Based on these results in advanced/recurrent malignant germ cell tumors of the ovary, the authors concluded that cisplatin based therapy is superior to previous regimens. They further stated that cisplatin- based chemotherapy will cure a substantial number of patients with malignant germ cell tumors.[39]
In 1994, the GOG reported on second-look operations in patients with malignant germ cell tumors of the ovary.[40] This report included patients from GOG protocol 45 as well as patients from later protocols (GOG #78 and GOG #90). Based on the findings of second look surgical reassessment procedures in 117 patients with malignant germ cell tumors, the following recommendations were made by the GOG authors: 1) patients with completely rsected germ cell malignant tumors rarely, if ever, benefit from sec ond-look surgery; 2) patients with advanced incompletely resected malignant germ cell tumors that do not contain immature teratoma elements rarely, if ever, benefit from second look surgery; 3) patients with incompletely resected malignant germ cell tumors containing teratoma elements have a substantial likelihood of benefiting from surgery to include the resection of residual tumor. They further recommended that VAC chemotherapy be considered in these patients with residual disease found at second-look surgical reassessment.[40]

GOG #90 evaluated the effectiveness of induction chemotherapy with cisplatin, etoposide and bleomycin (BEP) followed by consolidation with vincristine, actinomycin, and cyclophosphamide (VAC) in previously untreated patients with advanced stage ovarian germ cell tumors. The study also was to eval- uate the effect of BEP chemotherapy in patients with recurrent or progressive disease during or after previous non-platinum containing chemotherapy. Publications related to this study were published in the early 1990s.[41] This study population, analyzed with two earlier GOG studies (GOG #45 and #78) demonstrated that second-look laparotomy was not necessary in patients with completely resected disease initially or in patients with advanced disease that did not contain teratoma. However, the procedure seemed to be of some value in patients with incompletely resected tumors containing elements of teratoma.[42]

Sex Cord Stromal

Between 1971 and 1981, there were two other GOG studies of non-epithelial ovarian tumors. Protocol 13 evaluated VAC chemotherapy and whole abdominal irradiation in ovarian sarco- mas and protocol 14 evaluated chemotherapy and irradiation in malignant stromal tumors of the ovary.[43,44] Of the ovarian sarcoma patients in protocol 13, there was very inconsistent therapy and the main value of the study is as a registry to document the poor survival of these patients. Only three of six early stage I and II pa- tients survived more than three years and only one of 24 patients with stage III and IV survived more than three years.[43] Protocol 14 has only been published in abstract form.[44] Fifty-five patients with malignant stromal tumors were evaluable and were treated following surgery with some combination of irradiation and chemotherapy with dactinomycin, 5 flurouracil and cyclophos- phamide (AcFuCy). Although no therapeutic conclusions were possible due to the heterogeneity of cell types and stages, there were some complete responses with chemotherapy in patients with measurable disease and one complete response in a recurrent pa- In addition, GOG 115 evaluated the efficacy of bleomycin, etopo- side (VP-16), and cisplatin (BEP) chemotherapy in patients with malignant tumors of the ovarian stroma of the ovary as a first-line regimen for patients with histologically confirmed stage II – IV disease with incompletely resected disease, recurrent, or persistent tumor. The study was opened in April 1991 and closed in April 1997. The combination of BEP appeared active for first- line chemotherapy of malignant ovarian stromal tumors.Of patients with recurrent disease, 21 of 41 (51%) were progression free. Age and measurable disease were identified as risk factors. Seventy-five patients were entered on the study. Two bleomycin-related deaths occurred in 1992 and the study accrual was temporarily suspended until the dose and schedule of bleomycin was changed. Grade IV myelotoxicity was reported in 61% of patients. Limiting the bleomycin dose to 30 units per treatment course and to less than 120 units total dose avoided serious pulmonary morbidity.[45]

GOG 264 was designed to assess the activity of paclitaxel and carboplatin with respect to progression free survival (using bleomycin, etoposide, and cisplatin (BEP) as a reference) for newly diagnosed advanced stage (stage 2A to 4) or recurrent chemo-naïve ovarian sex cord stromal tumors. A total of 63 patients were accrued to the trial at the interim futility analysis, with no identified improvement in PFS with carboplatin and paclitaxel, although carboplatin and paclitaxel were associated with an improved safety profile. In June 2020, the study was closed to accrual following a pre-planned interim analysis indicating the the protocol-defined thresholds for continuing the study were not met. Furthermore, GOG 264 did not meet projected accrual goals following

activation (NCT01042522).

Older Patients

GOG 273 was a prospective observationa study of women with advanced stage ovarian cancer. This trial was designed to evaluate the pharmacokinetics of chemotherapy in elderly patient populations (defined as greater than 70 years of age) as well as impact on quality of life. This trial enrolled patients ≥ 70 years of age, with stage 1 to 4 ovarian, fallopian tube or primary peritoneal cancer. Patients were treated in three cohorts: single-agent carboplatin, every three week paclitaxel with carboplatin and weekly paclitaxel with every three week carboplatin. The study findings comparing CP (Carboplatin AUC 5, Paclitaxel 135mg/m2) to single C (Carboplatin AUC 5), were reported in 2017. Both regimens were adminsitered every 3 weeks, either after primary surgery or as neoadjuvant chemotherapy (NACT) with instrumental activities of daily living (IADL) and quality of life assessments performed at baseline, pre-cycle 3, and post-cycle 4.[92]

A total of 212 women were enrolled, 152 selecting CP and 60 selecting C. Those who selected CP had higher baseline IADL scores ($p<0.001$). After adjusting for both age and performance status, baseline IADL was independently associated with the choice of regimen ($p=0.035$). The baseline IADL score was not associated with completion of four cycles of chemotherapy without dose reduction or delays ($p=0.21$), but was associated with completion of four cycles of chemotherapy regardless of dose reduction and delay ($p=0.008$) and toxicity, with the odds ratio (OR) of grade 3+ toxicity decreasing 17% (OR: 0.83; 95%CI: 0.72-0.96; $p=0.013$) for each additional activity in which the patient was independent. After adjustment for chemotherapy regimen, IADL was also associated with overall survival ($p=0.019$) for patients receiving CP.

Of note, the third weekly paclitaxel plus carboplatin arm of the trial was then added at a later date, as a single arm study. The primary objective of this arm of the trial was to xplore the association between a baseline Geriatric Risk Score (GRS) and the patient's ability to complete four cycles of carboplatin q3week and paclitaxel qweek without dose reduction or >7-day treatment delays and to estimate the percentage of patients who are able to complete 4 cycles of chemotherapy. Findings from this arm suggested that weekly paclitaxel (60 mg/m2)plus carboplatin (AUC 5) was well tolerated. Desite an approximate 6% grade 3 or greater adverse event rate, almost all patients completed four cycles of treatment, 66% without dose reduction or more than 7-day delay. Twenty nine% of patients required a dose adjustment.

Conclusions

The GOG foundation continues to play an important role in defining the standard of care for the management of ovarian cancer. Through innovative trial design, the development of novel drugs and drug combinations as well as the identification of druggable molecular abberations, we have seen an improvement in oncologic outcomes for these patients. This is perhaps best expemplified in the the development, study and ultimaty FDA approval fo PARPi maintenance for newly diagnosed BRCAmut and HRD positive patient popultations. Importantly, although significant gains have been achieved in the front-line setting, the GOG FOundation remains committed to advancing the science and improving outcomes for patietns with HRD test negative (HRp) ovarian cancer, and in botht he platinum sensitive recurrent and platinum resistant recurrent settings. As reviewed, there are multiple active studies, with various therapeutic targets that may afford patients alternate treatment strategies. Ultimately, it is with this shared vision of scientific discovery that the GOG Foundation is committed to advancing outcomes in the ovarian cancer arena.

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