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Historical Perspective

# Shaping the standard of care in ovarian cancer management: A review of Gynecologic Oncology Group (GOG)/NRG oncology clinical trials of the past twenty years

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## HIGHLIGHTS

- The GOG/NRG Oncology has led the evolution of ovarian cancer treatment through clinical trials.
- The GOG/NRG Oncology has adapted to the changing landscape of cancer therapy.
- Active GOG/NRG Oncology trials may radically change the paradigm of how we treat ovarian cancer.

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## ABSTRACT

The Gynecologic Oncology Group (GOG), now part of the NRG Oncology network since the re-alignment of the National Clinical Trials Network in 2014, has played a fundamental role in creating the standard of care for women with ovarian cancer. GOG/NRG Oncology has had a series of achievements that have contributed to how we treat this disease; the approval of bevacizumab in frontline therapy, defining the role of intraperitoneal chemotherapy, optimal chemotherapy for early stage disease and the role of surgery in primary and recurrent disease management. Going forward, GOG/NRG Oncology is positioned to meet the ever changing knowledge that we have about the molecular background of this disease and the expanding repertoire of drugs/interventions in development.



## 1. Introduction

There will be a projected 22,240 cases of ovarian cancer and 14,070 deaths in the United States in 2018 [1]. Despite advances in the areas of targeted therapy and molecular biology, the prognosis for women diagnosed with advanced stage disease remains guarded, with only mild disease specific improved survival over the past decades. As we have learned from The Cancer Genome Atlas project [2], ovarian cancer is a molecularly diverse family of diseases requiring unique treatment strategies. With this diversity, however, comes opportunity for newer interventions in the field of targeted therapeutics. Traditionally, treatment trials have been distributed by stage, amount of residual disease and cell type. More recently, ovarian cancer clinical trials have adapted to the increasing knowledge of molecular mechanisms of certain cell types and the prevalence of these newer targeted strategies.

The success of the Gynecologic Oncology Group (GOG)/NRG Oncology ovarian cancer portfolio is manifest in studies that have shaped our current standard of care. The approval of bevacizumab in front line therapy, the role of intraperitoneal (IP) chemotherapy, further support for the use of bevacizumab in platinum sensitive recurrent disease and helping to define the role of surgery in front line and recurrent disease are some examples. The purpose of this manuscript is to review the National Cancer Institute (NCI) sponsored ovarian cancer trials of the GOG/NRG Oncology over the past twenty years. Some trials prior to that time frame will be referenced for their historical context. Although GOG/NRG Oncology has been active in the treatment of rarer tumor subtypes, such as germ cell and stromal tumors, the focus of this will be on epithelial ovarian cancer. In addition, the role of primary cytoreductive surgery has been the subject of a recent manuscript by Schorge, et al., in this journal [5] and will not be further reviewed. This historical perspective will review early stage trials, front line and maintenance therapy for advanced stage disease (intravenous and intraperitoneal), treatment of the elderly as an example of a special population

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investigation, the role of interval and secondary cytoreductive surgery, phase 1 trials and the treatment of recurrent disease.

## 2. Early stage ovarian cancer

Earlier trials of the GOG had established the utility of chemotherapy in the early stage population. The conclusions of these studies also demonstrated that patients with well-staged, stage IA or IB disease, with well or moderately differentiated disease likely did not benefit from chemotherapy, focusing the enrollment in future trials to higher risk, early stage disease [6,7]. GOG protocol 95 opened in 1986 as a prospective randomized trial of intraperitoneal $P^{32}$ compared with cyclophosphamide/cisplatin chemotherapy in women with early-stage ovarian cancer at high risk for recurrence. Eligible patients were surgically-staged with stage IA grade 3, IB grade 3, stage IC, or completely resected stage II ovarian cancer. A total of 251 patients were randomized between 1986 and 1994. The cumulative incidence of recurrence at 10 years was 35% for patients receiving IP $P^{32}$ and 28% for those receiving cyclophosphamide/cisplatin ($p = 0.15$). The death rate for patients treated with cyclophosphamide/cisplatin was 17% lower than for patients treated with IP $P^{32}$. The authors concluded that although there were no statistically significant differences in survival, the lower cumulative recurrence seen with cyclophosphamide/cisplatin and the increased toxicity of IP $P^{32}$ administration made the platinum-based combination the preferred adjuvant therapy for early ovarian cancer patients [8]. This trial was important in introducing cisplatin based chemotherapy to the treatment of ovarian cancer. Due to the consistent improvement of response and survival seen with the replacement of cyclophosphamide with paclitaxel in advanced-staged ovarian cancer, the next GOG trial for early-stage ovarian cancer was GOG 157. This study compared carboplatin and paclitaxel 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. The recurrence rate was 24% lower with six versus three cycles ($p = 0.18$). 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 epithelial ovarian cancer, but are associated with more toxicity [9]. A more recent analysis of survival based on histologic subtype demonstrated a statistically improved 5 year recurrence free survival (83 vs 60%, $p = 0.007$) favoring 6 cycles of therapy in patients with high grade serous tumors [10]. The appropriate number of cycles of therapy for early stage disease remains a source of debate and controversy.

Further analysis of the 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 [8,9]. GOG 95 reported that the 10-year accumulative 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, incorporate these patients into trials with advanced-stage patients.

The most recent trial for high-risk, early-stage ovarian cancer 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 and carboplatin chemotherapy with or without 24 weekly doses of paclitaxel maintenance chemotherapy [11]. This trial enrolled 571 patients of which 542 were evaluable for the study endpoints from 1998 to 2006. There was no benefit for the addition of maintenance paclitaxel compared to the control arm in terms of five year recurrence free survival or 5 year OS. There were higher rates of peripheral neuropathy, infection/fever and dermatologic events with the addition of maintenance paclitaxel.

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 trials for this patient population. Pertinent details of these early stage trials are presented in Table 1.

## 3. Front line therapy for advanced stage disease-intravenous therapy

Historically, the GOG separated patients with advanced stage ovarian cancer into optimally debulked or suboptimally debulked clinical trial populations. This was based on evidence supporting an increase in progression free survival (PFS) and overall survival (OS) based on the amount of residual disease at the time of surgical cytoreduction [12,13]. The development of neoadjuvant chemotherapy strategies and a focus on trials driven by histology or biomarkers of susceptibility has rendered the amount of residual disease to a stratification factor and less an inclusion/exclusion criteria. For the purposes of this review, the amount of residual disease will be mentioned but the focus will be on the therapies chosen to be studied.

Based on promising phase II data [14], the GOG conducted two consecutive randomized phase III trials assessing the potential value of paclitaxel as first line treatment in ovarian cancer. 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 ovarian cancer patients with residual disease great than 1 cm in diameter. The results of GOG 111 demonstrated a superior outcome for the paclitaxel containing arm in terms of response rate (77% vs 64%), risk of progression and risk of death [15].

However, before the results of that trial were available, the GOG initiated protocol 132 in a similar patient population. GOG 132 randomly assigned patients to single-agent cisplatin or paclitaxel or the combination of cisplatin/paclitaxel. Between 1992 and 1994, 648 eligible patients were enrolled on the trial. The response rate (67% vs 42%) and PFS favored the cisplatin containing treatment regimens [16]. The authors concluded that cisplatin alone or in combination with paclitaxel yielded a superior response rate and progression-free survival relative to paclitaxel. 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.

Building upon the results of GOG 111 and 132, GOG 158 compared carboplatin and paclitaxel over 3 h versus cisplatin and a 24-hour infusion of paclitaxel. Eligible patients had advanced ovarian cancer with no residual disease >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 authors found that gastrointestinal, renal and metabolic toxicity, as well as grade 4 leukopenia, were significantly more frequent in the cisplatin/paclitaxel arm [17]. The relative risk of progression and death for the carboplatin plus paclitaxel arm was not inferior to paclitaxel and cisplatin. The authors concluded that for patients with advanced ovarian cancer, 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.

The optimal length of paclitaxel administration was further explored in the front line setting in GOG 162. In this study, 293 patients with suboptimally resected stage II or IV ovarian cancer were randomly assigned to intravenous (IV) cisplatin with either paclitaxel administered IV over 24 or 96 h. The use of prolonged 96 h IV paclitaxel provided no additional benefit in terms of PFS or OS relative to the 24 h infusion.

GOG 182 built upon the combination of carboplatin and paclitaxel chemotherapy to assess new active agents in front-line therapy in regimens incorporating sequential doublet and triplet treatment strategies.

**Table 1**
Early stage trials.

| Protocol | Stages | Treatment | Proportion disease free | Proportion alive | RR/HR disease free | RR/HR alive | Conclusion |
|---|---|---|---|---|---|---|---|
| GOG 95 | IA or IB grade 3, IC or completely resected stage II | Intraperitoneal $P^{32}$ Cisplatin/Cytoxan IV | 65% 72% @10 yrs. | Not enumerated | Referent RR = 0.708 (95% CI 0.44 to 1.14) | Referent 0.83 ($p = 0.43$) | Lower rates of recurrence and toxicity favor cisplatin/cytoxan arm |
| GOG 157 | IA or IB, grade 3, clear cell, IC and optimally resected II | P/C x 3 cycles P/C x 6 cycles | 25.4% 20.1% @ 5 yrs. | 81% 83% @ 5 yrs. | Referent HR = 0.761 (95% CI 0.51–1.13) | Referent HR = 1.02 (95% CI 0.662–1.57) | Six cycles did not statistically improve the recurrence rate<br>Exploratory analysis demonstrates favorable outcome of six cycles in high grade serous tumors |
| GOG175 | Stage I, high risk | P/C P/C and Maintenance P | 77% 80% @ 5 yrs. | 85.4% 86.2% @ 5 yrs. | Referent HR = 0.807 (95% CI 0.565–1.15) | Referent HR = 0.781 (95% CI 0.522–1.17) | No improvement with addition of maintenance paclitaxel |

P=Paclitaxel, C=Carboplatin, yrs. = years, HR = hazard ratio, RR = relative risk, CI = confidence interval.

The additional agents included pegylated liposomal doxorubicin, gemcitabine and topotecan, and patients with optimal and suboptimal disease after surgery were eligible. Designed as a Gynecologic Cancer InterGroup trial, the trial enrolled 4312 women from 2001 to 2004. The patients were randomized to one of five separate IV regimens with paclitaxel and carboplatin serving as the control arm. The results demonstrated that the addition of a third cytotoxic agent provided no benefit in PFS or OS [18]. A unique strategy employed in this study was the statistical design of pairwise comparison to the reference arm, allowing for future evaluation of multiple experimental regimens against a single reference arm.

GOG 218 was the first prospective, randomized clinical trial in frontline advanced ovarian carcinoma of the GOG to utilize a targeted agent. Based upon the evidence that vascular endothelial growth factor (VEGF) and angiogenesis are important promoters of ovarian-cancer progression, the design of this study was to evaluate the addition of IV bevacizumab, a VEGF inhibitor, to standard front line therapy [4], similar to the International Collaboration on Ovarian Neoplasms (ICON) 7 trial [19]. GOG 218 randomized patients to IV paclitaxel and carboplatin chemotherapy for 6 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 bevacizumab throughout arm was statistically improved relative to the control arm. Based on the result of this trial, bevacizumab was Food and Drug Administration (FDA) approved in 2018 for use in combination with paclitaxel and carboplatin in the frontline management of women with advanced stage ovarian cancer [20].

Dose-dense, weekly paclitaxel, supported by data from a prior Japanese Gynecologic Oncology Group (JGOG) study demonstrating a statistically significant improvement in PFS when compared with every three week standard administration [21], led to the development of GOG 262. This trial randomized patients to carboplatin plus either dose dense, weekly paclitaxel versus standard every three week paclitaxel. The trial allowed for the use of bevacizumab every three weeks until progression at the patient and investigator's discretion, selected before randomization. This trial enrolled 692 patients of which 112 (16.1%) did not receive bevacizumab. PFS was not improved with the use of dose dense paclitaxel, differing from the JGOG study. Although not a primary endpoint of the study, in the cohort of patients not treated with bevacizumab, there was a statistically significant improvement in PFS with dose dense therapy (14.2 vs 10.3 months, HR = 0.62, 0.42–0.95), contributing to ongoing debate as to the optimal dosing regimen for paclitaxel in front line therapy. GOG 262 was also notable for inclusion of patients treated with neoadjuvant chemotherapy for the first time in GOG frontline treatment trials [22]. Patients in this trial were also eligible for the intergroup GOG/American College of Radiology Imaging Network (ACRIN) intergroup trial of perfusion CT imaging as a potential predictive biomarker for bevacizumab activity in ovarian cancer. Initial results in this limited population indicate that perfusion CT imaging may be an early biomarker of response in angiogenesis inhibitor based treatment regimens [23]. Pertinent details of the frontline intravenous trials can be found in Table 2.

## 4. Front line therapy-role of secondary cytoreductive surgery

In 1995, the European Organization for Research and Treatment of Cancer (EORTC) published a study demonstrating a benefit for secondary cytoreductive surgery during front line chemotherapy for patients with advanced stage ovarian cancer who had an initial suboptimal resection [24]. GOG 152 was designed to further evaluate this question. Patients with stage III or IV ovarian cancer who underwent a suboptimal (>1 cm residual) resection were randomly assigned after three cycles of chemotherapy to either secondary cytoreduction followed by completion of their front line chemotherapy or completion of therapy without surgery. The results demonstrate that the addition of surgery vs chemotherapy alone yielded no benefit in terms of PFS (10.5 vs. 10.7 months, HR = 1.07 (0.87–1.31)) or OS (33.9 vs. 33.7 months, HR = 0.99 (0.79–1.24)) [25].

## 5. Front line therapy for advanced stage disease– intraperitoneal chemotherapy

The GOG has been a leader in the development of intraperitoneal chemotherapy for advanced stage ovarian cancer. There have been four randomized phase III studies evaluating this strategy, with the results of the first three trials leading to the 2006 NCI Clinical Alert [3]. Gynecologic Oncology Group trial 104/Southwestern Oncology Group (SWOG) 8501 was a phase III trial evaluating IP chemotherapy for advanced, optimally debulked ovarian cancer. This study compared IV cisplatin and cyclophosphamide to IP cisplatin and IV cyclophosphamide. Eligibility for this trial included all patients with stage III ovarian cancer with no residual lesion measuring >2 cm after surgery. Results demonstrate that the intraperitoneal arm was associated with a statistically significant improvement in OS [26]. Since the control arm did not contain paclitaxel, it was suggested that the study lacked relevance to contemporary treatment planning.

GOG 114 compared IV cisplatin and paclitaxel versus high dose IV carboplatin every 28 days times two cycles followed by IP cisplatin and IV paclitaxel. The study was limited to patients who had stage III disease with less than or equal to 1 cm of residual tumor following surgery. Median PFS was statistically significantly improved in the IP arm. There was a borderline improvement inOS [27]. Although the PFS

**Table 2**
Frontline intravenous trials.

| Protocol | Patients | Debulking | Treatment | PFS | RR/HR PFS | OS | RR/HR OS | Conclusion |
|---|---|---|---|---|---|---|---|---|
| GOG 111 | Suboptimal Stages III/IV | Suboptimal (>2cm residual) | Cp/Cytoxan<br>Cp/P | 13 mo<br>18 mo | Referent<br>0.7 (95% CI 0.5–0.8) | 24 mo<br>38 mo | Referent<br>0.6 (95% CI 0.5–0.8) | Addition of P improves outcomes |
| GOG132 | Suboptimal Stages III/IV | Suboptimal (>2 cm residual) | Cp/P<br>Cp<br>P | 14 mo<br>16 mo<br>11 mo | Relative hazard for progression in P vs. Cp = 1.41 (95% CI 1.15–1.73)<br>Relative hazard for progression in Cp/P vs. Cp = 1.06 (95% CI 0.929–1.42) | 25.9 mo<br>30.2 mo<br>26.3 mo | Relative hazard for death in P vs. Cp = 1.15 (95% CI 0.929–1.42)<br>Relative hazard for death in Cp/P vs. Cp = 0.99 (95% CI 0.795–1.23) | Cisplatin containing arms superior to paclitaxel alone<br>Establishes cisplatin/paclitaxel as standard |
| GOG 158 | Optimal Stage III | Optimal (<1cm residual) | P/Cp<br>P/C | 19 mo<br>21 mo | Referent<br>0.88 (95% CI 0.75–1.03) | 48.7 mo<br>57.4 mo | Referent<br>0.84 (95% CI 0.70–1.02) | Non-inferiority study establishes P/C as standard |
| GOG 162 | Suboptimal Stage III/IV | Suboptimal | 24 h P/Cp<br>96 h P/Cp | 1.03 yrs.<br>1.05 yrs | Referent<br>1.00 (95% CI 0.784–1.28) | 2.49 yrs.<br>2.54 yrs | Referent<br>1.12 (95% CI 0.860–1.45) | No benefit to prolonged P infusion |
| GOG182-ICON | Stage III/IV | Optimal and Suboptimal | P/C<br>P/C/G<br>P/C/PLD<br>T/C– > P/C<br>G/C– > T/C | 16.0 mo<br>16.3 mo<br>16.4 mo<br>15.4 mo<br>15.4 mo | Referent<br>1.028 (95% CI 0.984 1.066 1.037) | 44.1 mo<br>44.1 mo<br>44.2 mo<br>40.2 mo<br>39.6 mo | Referent<br>1.006 (95% CI 0.885–1.144)<br>0.952 (95% CI 0.836–1.085)<br>1.051 (95% CI 0.925–1.194)<br>1.114 (95% CI 0.982–1.264) | Addition of third chemotherapy agent did not yield clinical benefit |
| GOG218 | Stage III/IV | Suboptimal and Optimal III/IV | P/C<br>P/C/B<br>P/C/B- > B | 10.3 mo<br>11.2 mo<br>14.1 mo | Referent<br>0.908 (95% CI 0.795–1.040)<br>0.717 (95% CI 0.625–0.824) | 39.3 mo<br>38.7 mo<br>39.7 mo | Referent<br>1.036 (95% CI 0.827–1.297)<br>0.915 (95% CI 0.727–1.152) | Result supports use of bevacizumab in front line therapy |
| GOG262 | Stage III/IV | Optimal, Suboptimal and Neo-adjuvant | Q3wk P/C +/− B<br>DD P/C +/− B | 14.0 mo<br>14.7 mo | Referent<br>0.89 (95% CI 0.74–1.06) | 39.0 mo<br>40.2 mo | Referent<br>0.94 (95% CI 0.72–1.23) | DD P did not improve survival outcomes<br>Subset analysis suggests DD P of benefit in patients not receiving B |

P=Paclitaxel, C=Carboplatin, CP=Cisplatin, G = Gemcitabine, T = Topotecan, PLD = Pegylated Liposomal Doxorubicin, B=Bevacizumab DD = Dose Dense, PFS = progression-free survival, OS = overall survival wk. = week, mo = months, yrs. = years, RR = Relative Risk, HR = Hazard Ratio, CI = confidence interval, NR = Not Reported, hr = hour.

endpoint was statistically significant; questions were raised as to the contribution of the high dose carboplatin to this outcome.

GOG 172 compared IV paclitaxel and cisplatin versus IV paclitaxel and IP cisplatin and paclitaxel. Treatment on both arms was administered every three weeks for a total of six courses. As in GOG 114, the patients had optimal disease residual less than or equal to 1 cm after initial surgery. A total of 415 eligible patients were enrolled. There was a statistically significant improvement in OS. 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 IP group reported significantly worse quality of life prior to cycle four, as well as three to six weeks post-treatment; however, there were no significant differences in quality of life between the arms one year post-treatment [ 28].

GOG 252 was developed to further assess IP chemotherapy relative to dose dense weekly chemotherapy as well as evaluate the role of IP carboplatin. This trial randomized patients to three arms. The first arm was a modification of the intraperitoneal arm in GOG 172, reducing the IP cisplatin to a dose of 75 mg/m squared IP on day 2 for 6 cycles in the hopes of reducing toxicity. The other two arms utilized dose dense weekly IV paclitaxel with either IV (control arm) or IP carboplatin for 6 cycles. All arms included bevacizumab IV every three weeks for 21 cycles (cycles 2–22). A total of 1381 patients were enrolled. There was no statistically significant improvement in median PFS for the IP cisplatin versus the control arm (27.8 vs 26.8 mos., HR = 0.947, 0.808–1.11) and IP carboplatin versus the control arm (28.7 vs 26.8 mos., HR = 1.01, 0.858–1.18) [29]. Pertinent details of the IP trials are in Table 3.

## 6. Front line maintenance therapy

GOG 178, an intergroup trial with SWOG, was designed to evaluate the role of maintenance paclitaxel in women with advanced ovarian cancer, who had a clinically-defined complete response to platinum/paclitaxel based chemotherapy, with a primary endpoint of PFS and a secondary endpoint of OS. Patients were randomly assigned to either three or 12 cycles of single-agent IV paclitaxel administrated every 28 days. From 1999 to 2001, 262 eligible patients had 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 ($p = 0.0035$) [30]. With a protocol-specified early termination boundary of $p = 0.005$, SWOG's Data Safety Monitoring Committee discontinued the trial and allowed for crossover of the patients treated on the 3 cycle arm to the 12 cycle arm. The final OS analysis (potentially impacted by post closure cross-over to additional cycles of paclitaxel), revealed no benefit for the 12 versus the 3 cycle arm (53 vs 48 mos., $p = 0.34$) The lack of quality of life data, treatment related toxicity and the need for dose reductions were of concern in addition to the lack of an OS benefit.

**Table 3**
Frontline intraperitoneal trials.

| Study | Patients | Debulking | Treatments | PFS | HR PFS | OS | HR OS | Conclusions |
|---|---|---|---|---|---|---|---|---|
| GOG 104 | Stage III/IV | Optimal (<2cm residual) | C (IV)//Cyt (IV)<br>C (IP)//Cyt (IV) | N/A | N/A | 41 mo<br>49 mo | Referent<br>HR = 0.76 (95% CI 0.61–0.96) | IP arm superior<br>Lack of P impacts relevance |
| GOG 114 | Stage III | Optimal (<1cm residual) | P (IV)//C (IV)<br>Ca (IV) x2 then P (IV)//C (IP) | 22.2 mo<br>27.9 mo | Referent<br>HR = 0.78 (95% CI 0.66–0.940 | 52.2 mo<br>63.2 mo | Referent<br>HR = 0.81 (95% CI 0.65–1.00) | Borderline OS improvement<br>IP regimen not routinely adopted |
| GOG 172 | Stage III | Optimal (<1cm residual) | P (IV)//C (IV)<br>P (IV)//C (IP)//P (IP) | 18.3 mo<br>23.8 mo | Referent<br>HR = 0.80 (95% CI 0.64–1.00) | 49.7 mo<br>65.6 mo | Referent<br>HR = 0.75 (95% CI 0.58–0.97) | Dramatic OS improvement tempered by toxicity concerns |
| GOG 252 | Stage III/IV | Optimal/Suboptimal | DD P (IV)//Ca (IV)//B (IV)<br>DD P (IV)//Ca (IP)/B(IV))<br>P (IV)//C (IP)//P (IP)//B (IV) | 24.9 mo<br>27.4 mo<br>26.2 mo | Referent<br>HR = 0.925 (95% CI 0.802–1.07)<br>HR = 0.977 (95% CI 0.847–1.13) | Pending Final Manuscript | N/A | No benefit to IP therapy |

C=Cisplatin, Cyt = Cytoxan, P=Paclitaxel, Ca = Carboplatin, B=Bevacizumab, IV = intravenous, IP = intraperitoneal, DD = dose dense weekly, HR = hazard ratio, PFS = progression-free survival, OS = overall survival, mo = months, CI = confidence interval, cm = centimeters.

GOG 212 differed from GOG 178 with a primary endpoint of OS and the use of a surveillance arm. Patients with a clinical complete response to front line paclitaxel and platinum based chemotherapy were randomly assigned to surveillance (S), every 28 day paclitaxel (P) or every 28 day CT-2103 (paclitaxel poliglumex) (PP) for a total of 12 cycles. A total of 1157 patient were enrolled from 2005 to 2014. OS was 54.8, 51.3 and 60 months respectively. The hazard ratio for survival of P vs S was 1.104 (0.884–1.38) and PP vs S was 0.979 (0.781–1.23), demonstrating a lack of benefit for the use of maintenance chemotherapy in this trial Although not the primary endpoint, PFS for the three regimens were 13.4, 18.9 and 16.3 months respectively P vs S HR = 0.793 (95%CI 0.666–0.921) and PP vs S HR = 0.847 (95% CI 0.721–0.995) [31].

## 7. Summary of front line ovarian cancer therapy

The GOG/NRG Oncology is instrumental to what we consider standard in the front line treatment of ovarian cancer: paclitaxel and carboplatin chemotherapy, IP chemotherapy, the use of bevacizumab and the evaluation of maintenance. Going forward, the focus of front line therapy will be on the development of smaller, randomized phase II trials with integrated or integral biomarkers. Neoadjuvant chemotherapy presents a unique opportunity for predictive biomarker assessment pre and post therapy. NRG GY007 (NCT 02713386) is an example of this and is an ongoing randomized phase II trial assessing the role of ruxolitinib, a JAK2 inhibitor, in combination with paclitaxel and carboplatin chemotherapy in patients undergoing neoadjuvant chemotherapy and is actively enrolling at the time of this publication.

## 8. Treatment of the elderly

Ovarian cancer occurs over a wide age spectrum with approximately 30% of all new diagnoses occurring in women over the age of 70. Strategies to ensure appropriate care for this special population are critical. Outcomes for elderly (age > 70) have generally been inferior to younger age populations due to the belief that elderly patients cannot tolerate standard treatments. However, this age group is more prone to the toxicities of therapy. GOG 273 was designed as a prospective trial for elderly women (age > 70) with advanced ovarian cancer. The primary objective was correlation of chemotherapy tolerance to pre-treatment Instrumental Activities of Daily Living (IADL). Secondary objectives included pharmacokinetics of chemotherapy in this group as well as quality of life impact. Results demonstrate that patients with a higher IADL score at baseline were more likely to complete 4 cycles of chemotherapy and less likely to experience grade 3 or higher toxicity [32].

GOG/NRG Oncology continues to evaluate strategies to reduce morbidity in these patients, specifically in regards to the surgical component of therapy. NRG CC002 (NCT 02315469) is a prospective trial of preoperative assessment and postoperative outcome in elderly patients undergoing surgery for ovarian cancer. Enrollment is complete for this trial and final results are pending.

## 9. Recurrent disease

The success of secondary cytoreductive surgery (SCS) in patients with recurrent ovarian cancer has been based mainly on retrospective cohort studies in the literature. Factors predicting success include the length of time since completion of front line therapy, amount and distribution of disease, presence or absence of ascites, Ca-125 level and performance status among others. GOG 213, in addition to evaluating the impact of the addition of bevacizumab to paclitaxel and carboplatin in patients with platinum sensitive recurrent disease, contained a surgical randomization in patients who were considered amenable to resection. Four hundred and eighty five women with investigator determined resectable disease were randomly assigned to surgery or not. The median OS for surgery versus not was 53.6 vs 65.7 months (HR = 1.28, 0.92–1.79). Although shown to be safe, SCS did not improve overall survival [33].

GOG/NRG Oncology has a critical role in drug development for patients with recurrent disease. Earlier trials of the GOG evaluated the role of multiple chemotherapy agents, such as cisplatin and paclitaxel, in a series of mainly single agent trials. There have overall been >100 trials completed for recurrent ovarian cancer and a summary of these trials would exceed the prescribed length of this manuscript, The focus of this article will be on more recent developments in the treatment of recurrent disease, including angiogenesis inhibitors, poly (ADP-ribose) polymerase (PARP) inhibitors and immunotherapy, studied within GOG/NRG Oncology and their current and potential impact on the standard of care for recurrent disease.

GOG 170D was a phase II trial of bevacizumab in recurrent platinum sensitive or resistant ovarian cancer. This trial enrolled 62 patients from 2002 to 2004 and utilized a novel endpoint of percent progression free at 6 months, likely reflecting a more relevant efficacy measure for this drug and its ability to stabilize disease. There was a 21.0% response rate and 40.3% of patients were progression free for at least 6 months in this patient population [34]. These promising results led to the continued development of this treatment in ovarian cancer.

Concurrent with GOG 218 in the further development of bevacizumab, GOG 213 was a randomized trial of paclitaxel and carboplatin with or without bevacizumab in women with platinum sensitive, recurrent ovarian cancer. Six hundred and seventy four patients were enrolled from 2007 to 2011. The addition of bevacizumab yielded a statistically significantly improved PFS. The benefit of bevacizumab in primary endpoint of OS is controversial. Prior to any post hoc correction of the platinum free interval, there was no OS benefit (42.2 vs 37.3 months, HR = 0.829, 0.683–1.005). However, in a post hoc sensitivity analysis correcting for platinum free interval, the result was significant [35].

GOG 186I studied the addition of fosbretabulin tromethamine, a vascular disrupting agent, to bevacizumab compared to bevacizumab alone in a randomized phase II trial. One hundred and seven patients were enrolled. There was a statistically significant improvement in PFS for the experimental arm. The response rate for the combination arm was 35.7% vs 28.2% in the control arm [[36]]. Unfortunately, a randomized phase III trial of chemotherapy and bevacizumab with or without fosbretabulin tromethamine (NCT 02641639) was terminated due to a lack of efficacy in the experimental arm.

The mechanism of PARP inhibition and the variety of effective drugs in this class are well known in ovarian cancer. GOG/NRG Oncology has been involved in the development of two of these drugs, veliparib and olaparib. GOG evaluated the role of veliparib in a phase I dose escalation study, GOG 9923, looking to establish the optimal dosing strategy of PARP inhibition with a variety of front line chemotherapy strategies. Although the combination of chemotherapy and veliparib was not further developed within GOG/NRG Oncology, this trial, enrolling 431 patients in six dosing cohorts, demonstrated the ability GOG/NRG Oncology to conduct this type of trial through its phase I subcommittee [37]. This capability is increasingly more evident through the use of phase I institutions in early safety lead-ins of trials with newer agents in novel combinations. Veliparib was evaluated for single agent activity in GOG 280, a phase II trial in women with known germline BRCA mutations and recurrent ovarian cancer. There were 50 evaluable patients of which 60% were platinum resistant. The overall response rate was 26%, with a rate of 20% in platinum resistant and 35% in platinum sensitive patients. The median PFS was 8.2 months [38].

NRG GY004 (NCT02446600) and 005 (NCT02502266) are two trials that may change the paradigm of how we treat recurrent disease. Based on encouraging data for the combination of olaparib and cediranib from the trial of Liu, et al. [39], NRG GY004 is a prospective, randomized phase III trial of olaparib, olaparib and cediranib, and standard platinum based chemotherapy in women with platinum sensitive recurrent disease. This trial has completed enrollment and awaits the result for the primary endpoint of PFS. The results of this trial may establish an oral targeted strategy of treatment versus cytotoxic chemotherapy in platinum sensitive recurrence, a departure from a well-established standard. NRG GY005 is also exploring non-cytotoxic strategies in platinum resistant disease, evaluating olaparib, cediranib, the combination of olaparib and cediranib and standard agent chemotherapy in platinum resistant disease. Enrollment in that trial is ongoing.

Immunotherapy represents another strategy in the treatment of recurrent disease. NRG GY003 is a randomized trial of nivolumab, a programmed cell death 1 (PD-1) inhibitor with or without ipilimumab, a CTLA-4 inhibitor, in recurrent ovarian cancer. There were 100 evaluable patients. There was a statistically significant improvement in PFS for the combinationarm. The response rate within 6 months also favored the combination (31.4 vs 12.2%, OR 3.28, 1.90-∞) [40].

NRG GY009 (NCT02839707) is an ongoing trial evaluating the role of atezolizumab, an antibody to programmed cell death ligand 1 (PD-L1) in platinum resistant recurrent ovarian cancer. This prospective randomized phase III trial compares the addition of atezolizumab, bevacizumab, or the combination of the two agents to standard pegylated liposomal doxorubicin chemotherapy. The primary endpoint is PFS and this trial is actively enrolling. This trial included a safety lead-in, utilizing the phase I mechanism to assess the safety of the experimental strategies within the context of a larger trial. So much of what will be evaluated in future recurrent disease trials will require this type of flexible design and GOG/NRG Oncology has a proven capacity to do this. NRG GY017 (NCT 03602586) is another example of GOG/NRG Oncology's commitment to immunotherapy as a treatment strategy in ovarian cancer. This is a trial combining Pembrolizumab, a PD-L1 inhibitor and with the immune modulator epacadostat, a indoleamine 2,3-dioxygenase-1 (IDO1) inhibitor, in recurrent clear cell ovarian carcinoma.

NRG GY001 is a phase II trial of cabozantanib, a small molecule inhibitor of the tyrosine kinases, c-Met and VEGFR2, in clear cell carcinoma. Unfortunately, no responses were seen in the 13 patients treated in this unselected population [41]. GOG 281 is a randomized phase II trial comparing trametinib, a MEK 1 and 2 inhibitor, versus physician choice standard therapy in recurrent low-grade serous carcinoma. This trial has completed enrollment and final results are pending. Both of these trials are example of the ability of GOG/NRG Oncology to enroll patients onto rare histologic subtypes of ovarian cancer.

**Table 4**
Recurrent disease treatment trials.

| Trial | Phase | Eligibility criteria | Regimens | PFS/RR | Conclusion |
|---|---|---|---|---|---|
| GOG 213 | III | Platinum sensitive | P or G/C<br>P or G/C with Bevacizumab | 10.4 mo<br>13.8 mo<br>HR = 0.628 (95% CI 0.534–0.739) | Addition of bevacizumab improves outcome.<br>OS benefit 42.2 vs 37.3 mo. (HR = 0.823, 95% CI 0.680–0.996) |
| GOG 170D | II | Platinum sensitive/resistant | Bevacizumab | 40.3% progression free at 6 months, 21.0% RR | Results support further development of bevacizumab in ovarian cancer |
| GOG 186G | II | Platinum sensitive/resistant | Bevacizumab<br>Bevacizumab/Everolimus | 4.5 mo<br>5.9 mo<br>HR = 0.95 (95% CI 0.66–1.37) | Addition of everolimus does not improve outcome |
| GOG 186I | II | Platinum sensitive/resistant | Bevacizumab<br>Bevacizumab/Fosbretabulin | 4.8 mo<br>7.3 mo<br>HR = 0.69 (95% CI 0.47–1.00) | Addition of fosbretabulin improves outcome |
| GOG 186F | II | Platinum sensitive/resistant | Docetaxel/Trabectedin | 4.5 mo<br>30% response rate | Regimen active |
| NRG GY001 | II | Recurrent Clear Cell Carcinoma | Cabozantinib | 0% response rate | Cabozantinib not active in this unselected cohort |
| NRG GY003 | II | Platinum sensitive/resistant | Nivolumab<br>Nivolumab/Ipilimumab | 2.0 mo<br>3.9 mo<br>HR = 0.599 (95% CI 0.388–0.925)<br>31.4% RR in combination arm | Improvement in outcome supports continued development of regimen |
| GOG 280 | II | Platinum sensitive/resistant | Veliparib | 8.2 mo<br>26% RR | Demonstrated activity of Veliparib in this selected population |

P=Paclitaxel, G = Gemcitabine, C=Carboplatin, PFS = progression-free survival, RR = response rate, HR = hazard ratio, CI = confidence interval, mo = months.

**Table 5**
Active trials in ovarian cancer.

| Trial | Eligibility criteria | Regimens | Primary endpoint |
|---|---|---|---|
| NRG GY004 | Platinum sensitive recurrence | Olaparib<br>Olaparib/Cediranib<br>Platinum based chemotherapy | PFS |
| NRG GY005 | Platinum resistant recurrence | Olaparib*<br>Cediranib<br>Olaparib/Cediranib<br>Chemotherapy | PFS |
| NRG GY007 | Frontline patients undergoing neoadjuvant chemotherapy | Dose DenseWeekly Paclitaxel/Carboplatin<br>Dose DenseWeekly Paclitaxel/Carboplatin/Ruxolitinib | PFS |
| NRG GY009 | Platinum resistant recurrence | Pegylated Liposomal Doxorubicin/Bevacizumab<br>Pegylated Liposomal Doxorubicin/Bevacizumab/Atezolizumab<br>Pegylated Liposomal Doxorubicin/Atezolizumab | PFS |
| NRG GY017 | Recurrent Clear Cell Carcinoma | Pembrolizumab and Epacadostat | RR |
| GOG 281 | Recurrent low grade serous carcinoma | Trametininb<br>Physician choice therapy | PFS |

RR = response rate, PFS = progression-free survival.
*Olaparib arm dropped prior to phase III portion of trial.

Pertinent details of recurrent disease trials with reported outcomes described above and other examples of recurrent disease trials [42,43] can be found in Table 4. Table 5 summarizes ongoing trials not yet reported.

## 10. Phase I trials

Since inception, GOG/NRG Oncology has completed in excess of 30 phase I clinical trials in ovarian cancer. These trials for the most part have focused on the feasibility of drug combinations to be tested in later phase trials of which the following are examples for front line therapy. GOG 9917 [44] tested the feasibility of intraperitoneal carboplatin with intravenous paclitaxel both with and without intravenous bevacizumab, a regimen later used in GOG 252. GOG 9801 [45] evaluated the feasibility of intravenous carboplatin, paclitaxel and gemcitabine in front line therapy, eventually one of the regimens in GOG 182. GOG 9923, as cited previously, determined the maximal tolerated dose (MTD) for a phase 3 trial that was eventually conducted outside of the NCI funded GOG/NRG Oncology mechanism (NCT02470585).

In recurrent disease, GOG 9925 [46], which determined the MTD for the combination of pegylated liposomal doxorubicin with VTX 2337, a Toll-like receptor 8 agonist, and GOG 9928 [47], which determined the MTD for the combination of IP GEN-1, an IL-12 plasmid and IV pegylated liposomal doxorubicin are examples of non-cytotoxic strategies evaluated in combination with chemotherapy. GOG 9924 [48] evaluated the MTD of IP bortezomib and carboplatin, under the theory that bortezomib would help to overcome the role of platinum resistance.

## 11. Summary

GOG/NRG Oncology has helped to shape the standard of care in ovarian cancer treatment. It has done so by adapting to the changing landscape of ovarian cancer treatment driven by our understanding of the underlying biologic mechanisms of cancer, the biomarkers that help to predict response and the dramatic increase in available treatments. The currently active trials may drastically change the paradigm in how we treat recurrent disease. The evolving neoadjuvant platform, with the example of NRG GY007, will allow for expeditious exploration of new agents as they become available for frontline treatment. The role of immunotherapy will continue to be evaluated, with current concepts for frontline and recurrent disease in development, both in combination with chemotherapy as well as other targeted agents. This is not without challenges, as the overall number of available trials in ovarian cancer within GOG/NRG Oncology has decreased with the advent of the National Clinical Trials Network in 2014. However, with the proliferation of new concepts and a greater understanding of the biologic heterogeneity inherent in ovarian cancer GOG/NRG Oncology will continue to contribute to the improvement of outcomes and shape the standard of care for women affected by ovarian cancer.

### Conflict of interest statement

Dr. Paul DiSilvestro has received consultancy payments from Astra Zeneca and Tesaro outside of the submitted work.

## Author contributions

Conception and design, collection and assembly of data, data analysis and interpretation and manuscript writing and final approval by the author.

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