Clinical trial results continue to clarify optimal management of patients with ovarian cancer.

Current and Future Directions of Clinical Trials for Ovarian Cancer

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Background: The management of ovarian cancer includes a combination of surgery and chemotherapy. The majority of clinical trials have historically addressed questions pertaining to the selection, dosing, and schedule of chemotherapy agents.

Methods: In this report, a comprehensive review of the major clinical trials in ovarian cancer is performed. The increasing data and clinical experience in the management of ovarian cancer, as it sets the stage for currently active protocols and future clinical trial design, are emphasized.

Results: Paclitaxel plus carboplatin is the primary intravenous treatment strategy in the front-line setting. Recent data show an improvement in overall survival for intravenous dose-dense treatment. Multiple randomized controlled trials support the use of intraperitoneal treatment. For recurrent disease, a growing number of new agents including targeted therapeutics are now available. Increasingly, surgical approach, biologic targets, and quality of life endpoints are included in clinical trial design.

Conclusions: Over the last several decades, clinical trials have defined the current therapeutic approach for ovarian cancer. Paclitaxel with a platinum-based agent is currently the preferred front-line therapy, with encouraging data to support either dose-dense or intraperitoneal drug delivery. Future trials will determine the role of biologic agents and vaccine therapies, as well as their impact on quality of life.

Introduction

The management of ovarian cancer encompasses a combination of surgical resection and chemotherapy. Over the last several decades, clinical trial results have led to an evolution in the management of ovarian cancer. In 2006, for the first time, a median overall survival (OS) of greater than 5 years was reported among advanced-stage ovarian cancer patients treated in a randomized controlled trial setting.¹

Clinical trials continue to address important questions pertaining to the combination of surgery and chemotherapy, the identification of new targeted therapeutics, and the route and timing of chemotherapy administration. In addition, there is a growing interest in trial design that incorporates quality of life endpoints as well as tissue acquisition for translational studies to further identify the underlying mechanisms of ovarian cancer growth, metastasis, and development of chemoresistance. This report discusses current and future directions of ovarian cancer clinical trials, with an emphasis...
on the prioritization of future research efforts for this challenging disease.

Primary Treatment

Intravenous Treatment

Landmark studies have established paclitaxel plus carboplatin as the primary intravenous (IV) treatment strategy for epithelial ovarian cancer. A study by the Gynecologic Oncology Group (GOG 111) demonstrated a survival benefit of cisplatin and paclitaxel in comparison to cisplatin and cyclophosphamide.² This was followed by GOG 158, which demonstrated that carboplatin plus paclitaxel is at least as effective as cisplatin plus paclitaxel, but with less renal toxicity.³ These results prompted the Gynecologic Cancer Intergroup (GCIG) to publish consensus guidelines that favor carboplatin and paclitaxel as the comparator arm for future clinical trials.⁴

As new chemotherapy agents have been identified and shown activity for recurrent disease, GOG 182-ICON5 was established to determine if additional cytotoxic agents in the front-line setting would further extend progression-free survival (PFS) or OS.⁵ This 5-arm randomized controlled trial utilized paclitaxel and carboplatin IV every 3 weeks for 8 cycles as the control arm. Topotecan, gemcitabine, and pegylated liposomal doxorubicin were each evaluated either as a part of triple drug therapy or in sequential doublets. Interim analysis failed to demonstrate superiority of any of the experimental arms, and the trial was closed in 2004. Paclitaxel plus carboplatin remains the standard front-line IV therapy. Despite its negative results, this study was significant in its large-volume global accrual, and it sets the stage for future international cooperative group trials.

Recent studies have addressed the frequency of IV treatment. In a randomized phase III trial, a dose-dense regimen of weekly paclitaxel in combination with carboplatin every 3 weeks showed a statistically significant improvement in PFS: 28.0 months compared to a PFS of 17.2 months in patients receiving a standard 3-week dosing of both agents.⁶ OS at 3 years was also higher in the dose-dense group: 72.1% compared to 65.1% in the conventional treatment group (hazard ratio [HR] = 0.75; confidence interval [CI], 0.57–0.98). These results favor a dose-dense regimen; however, patient dropout due to toxicity was higher in the dose-dense group, primarily related to hematologic side effects.

During a similar study period, the GOG evaluated the addition of a targeted therapeutic, bevacizumab, to the standard IV paclitaxel/carboplatin regimen administered every 3 weeks. Bevacizumab is a monoclonal antibody that neutralizes the vascular endothelial growth factor (VEGF)-A, the predominantly active species of VEGF, and thereby inhibits angiogenesis. In GOG 218, paclitaxel and carboplatin IV every 3 weeks served as the control arm. The experimental arms included concurrent bevacizumab at 15 mg/kg, with one arm continuing bevacizumab as maintenance therapy for an additional 16 cycles after the primary chemotherapy regimen was complete. A preliminary announcement of GOG 218 demonstrated a benefit of treatment with bevacizumab but only when bevacizumab is continued as maintenance therapy. Results of this trial presented at the 2010 meeting of the American Society of Clinical Oncology (ASCO) reported a 3.8-month improvement in PFS.⁷ OS results are pending.

Intraperitoneal Treatment

Concurrent with the developments in IV treatment, intraperitoneal (IP) treatment has also been shown to be a valuable strategy. IP chemotherapy is designed to leverage the pharmacokinetic profile of chemotherapeutic agents and thereby deliver higher doses into the anatomic compartment that is at greatest risk for disease regrowth. The majority of IP treatment stays within the peritoneal compartment, with limited deep tissue penetration; therefore, it is indicated only for patients who have completed an optimal cytoreductive surgery. To date, three randomized controlled trials have been conducted by the GOG as well as several international studies that have shown a benefit of IP treatment among optimally debulked patients.³⁻⁶⁻¹³ GOG 172, the most recent GOG study, evaluated paclitaxel and cisplatin as either an IV only or as an IV/IP combination. A significant benefit in OS was identified: 65.6 months in the IP arm and 49.7 months in the IV only arm (Fig 1). This benefit in OS was demonstrated despite the fact that only 42% of patients were able to complete 6 cycles of IP treatment. Grade 3/4 toxicities were higher in the IP treated group. The substantial benefit in OS in this study, as well as the results of multiple prior studies identifying a benefit of IP treatment, led the NCI to issue a clinical alert that patients with newly diagnosed optimally debulked ovarian cancer should be considered for IP treatment.

Subsequent studies have sought to identify a dose and schedule with less toxicity than the GOG 172 trial. GOG 9916 and 9917 were opened to evaluate IP carboplatin. Konner et al.⁴ reported on a phase II trial from Memorial Sloan-Kettering Cancer Center using a modified 172 regimen in combination with bevacizumab. In comparison with GOG 172, the day 1 IV paclitaxel was modified from a 24-hour infusion to a 3-hour infusion, and the day 2 IP cisplatin dose was decreased from 100 mg/m² to 75 mg/m². The day 8 IP paclitaxel remained the same. With cycle 2, bevacizumab at 15 mg/m² was included on day 1 of treatment. At interim analysis, 80% of patients either had completed 6 cycles or were continuing on protocol with this IP regimen. Grade 3/4 toxicities occurred in approximately 10% of patients, with the exception of neutropenia, which occurred in 26% of patients. These data suggest that the addition of bevacizumab to this IV/IP regimen is feasible and preliminarily indicates a high rate of successful completion of IP therapy with limited toxicity.
Taken together, recent clinical trials suggest there may be a benefit from dose-dense paclitaxel as seen in the Japanese study and also in the trial design of GOG 172 that included paclitaxel on day 1 and day 8. The currently open GOG 252 trial takes into account issues pertaining to dose-dense therapy, IP therapy, and the inclusion of bevacizumab in front-line treatment in order to establish the most effective approach (Fig 2). It is anticipated that GOG 262 will open soon; this trial will address treatment options for suboptimally debulked patients with randomization to IV paclitaxel and carboplatin given every 3 weeks vs weekly paclitaxel. Both arms will include bevacizumab administered concurrently as well as maintenance therapy.

**Cytoreductive Surgery**

Cumulative data from multiple large retrospective studies have shown that optimal cytoreductive surgery prior to chemotherapy is associated with an improvement in OS.\(^1^5\)-\(^1^7\) The rationale for this is based on reduction of tumor burden and thereby the potential for developing chemoresistant disease, a reduction in poorly perfused tumor to enhance drug delivery, and an associated increase in the percent of tumor with a high mitotic index that is more susceptible to the effects of cytotoxic chemotherapy. However, there are limitations of the clinical eligibility for cytoreductive surgery based on a variety of factors including performance status, comorbidities, age, and disease distribution. For a patient unable to undergo a primary cytoreductive surgery, neoadjuvant chemotherapy has been given to reduce the disease burden prior to surgical resection. Recently, the European Organisation for Research and Treatment of Cancer (EORTC) conducted a prospective phase III study to evaluate primary debulking vs neoadjuvant chemotherapy in advanced-stage ovarian cancer patients and demonstrated no difference in OS.\(^1^8\) Notably, the median survival for both arms was approximately 30 months, much shorter than the 50 months reported for patients who completed optimal debulking in most prior studies. The potential for an inherent selection bias in the patient enrollment should be considered. In other words, patients enrolled in a trial randomized to undergo surgery or a more conservative approach may not include the best surgical candidates. The results of this single study are provocative and would benefit from confirmatory studies to support these findings. The GOG is currently discussing a plan to further evaluate the role of primary surgery vs neoadjuvant chemotherapy with selection criteria to better define surgical candidates and thereby allow for stratification of patient outcomes.

![Survival by Treatment Group - GOG 172](image-url)
Maintenance Therapies
At the completion of surgery and chemotherapy, the majority of patients will achieve a complete clinical remission. Instead of terminating treatment at this point, the concept of maintenance therapy is to continue a low-toxicity treatment in an effort to maintain the disease remission and thereby increase PFS and OS. In general, maintenance therapy involves continuing at least one of the agents used in the primary treatment strategy, and much focus has been placed on antiangiogenic strategies.

A study performed by the Southwest Oncology Group and the GOG examined the use of IV paclitaxel in patients with a complete response to upfront therapy. Patients were randomized to receive either 3 cycles or 12 cycles of maintenance IV paclitaxel. There was a PFS advantage of 7 months observed in patients receiving the 12-cycle arm. This study was terminated early and prevented definitive conclusions about the effectiveness of this treatment approach on OS. In Europe, Pecorelli et al found no improvement in PFS or OS in patients who received an additional 6 cycles of paclitaxel as consolidation treatment after complete response from initial therapy. The GOG currently has an ongoing study, protocol 212, with patients randomized to observation or monthly IV paclitaxel or CT-2103, a polyglutamated taxane. GOG 218 and ICON 7 are examining the use of bevacizumab in front-line therapy followed by a schema of maintenance dosing. GOG 218 has demonstrated a 3.8-month improvement in PFS for patients who received combination paclitaxel, carboplatin, and bevacizumab followed by maintenance bevacizumab compared to the study arms without maintenance therapy. It remains to be seen if this difference in PFS will be enough to offset the side effects and cost of treatment. OS data are not yet available.

Immunotherapy represents an exciting area of research and has been studied as a potential option for maintenance therapy. Vaccines have been developed to target areas of the CA-125 antigen, a protein produced by most epithelial ovarian cancers. Oregovomab is an immunoglobulin murine monoclonal antibody that binds to CA-125. Retrospective studies and phase II trials showed positive results for the use of oregovomab. However, a randomized controlled trial of patients in first clinical remission showed no benefit over placebo. A newer antigen being evaluated is MUC 16. The vaccine using MUC 16 as the target is an anti-idiotype vaccine. It is hoped

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**GOG 252**

*Phase A: Cycles 1-6*

- Paclitaxel 80 mg/m² IV over 1 hour days 1, 8 and 15
- Carboplatin AUC 6 IV on day 1
- Bevacizumab 15 mg/kg IV on day 1 beginning on cycle 2

*Phase B: Cycles 7-22*

- Paclitaxel 80 mg/m² IV over 1 hour days 1, 8 and 15
- Carboplatin AUC 6 IP on day 1
- Bevacizumab 15 mg/kg IV on day 1 beginning on cycle 2

- Paclitaxel 135 mg/m² IV over 3 hours day 1
- Cisplatin 75 mg/m² IP on day 1
- Paclitaxel 60 mg/m² IP on day 8
- Bevacizumab 15 mg/kg IV on day 1 beginning on cycle 2

- Bevacizumab 15 mg/kg IV on day 1 for cycles 7-22

- Weekly paclitaxel + q3wk IP carboplatin

- Modified q3wk IP

* Continue regimen every 3 weeks for 6 cycles of chemotherapy and a total of 22 cycles including bevacizumab unless toxicity or progression intervenes.

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Fig 2. — Schema of the current GOG 252 protocol evaluating IP cisplatin vs IP carboplatin and a comparator arm IV-only dose-dense treatment. All treatment arms include concurrent and maintenance bevacizumab dosing.
that such anti-idiotype vaccines will increase the immune response against the presented antigen. An international randomized phase III trial enrolled patients in a 2:1 fashion to receive this vaccine, and results are pending.26

Treatment of Recurrent Disease

While increasing numbers of patients with ovarian cancer are experiencing 5-year survival,1 90% of suboptimally debulked patients and 70% of optimally debulked patients relapse 18 to 24 months following primary treatment.27 Given the expanding number of active drugs and treatment regimens available, treatment selection for recurrent disease can be complex. Several important studies and ongoing clinical trials can help in guiding management.

Chemotherapy Options

Traditionally, patients with recurrent platinum-sensitive ovarian cancer, defined as a disease-free interval from completion of primary treatment of at least 6 months, have been re-treated with platinum-based chemotherapy, often in combination with another chemotherapeutic agent. In ICON 4, platinum-sensitive patients were randomized to receive a platinum-based regimen with or without a taxane. In the conventional platinum-based chemotherapy arm, 73% of patients received a single-agent platinum. In the taxane-containing arm, 90% received paclitaxel as part of a doublet (80% received paclitaxel and carboplatin, 10% received paclitaxel and cisplatin). Results demonstrated that patients assigned to receive a taxane, the majority of whom received this in combination with a platinum agent, experienced higher response rates, better PFS, and superior OS compared to those who received re-treatment with a single-agent platinum.28 Notably, not all patients had received the combination of paclitaxel and carboplatin in the front-line setting.

Cumulative toxicity from primary therapy, specifically neurotoxicity, can preclude re-treatment with paclitaxel and carboplatin, and therefore other platinum-based doublets have been explored. The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) conducted a randomized phase II trial (AGO OVAR 2.5) comparing single-agent carboplatin with the combination regimen of gemcitabine and carboplatin. The study showed that patients assigned to the gemcitabine/carboplatin group experienced a higher response rate and a superior PFS but no difference in OS. This study concluded that the doublet of gemcitabine and carboplatin was an acceptable treatment regimen for recurrent disease.29 Currently, the OCEANS trial is evaluating outcomes of gemcitabine and carboplatin in combination with bevacizumab.30

As an alternative strategy, the CALYPSO trial randomized patients to receive either the doublet of pegylated liposomal doxorubicin (PLD) and carboplatin vs paclitaxel and carboplatin.31 The study demonstrated an improvement in PFS for the PLD/carboplatin arm (median: 11.3 month vs 9.4 months; HR = 0.82; P = .005). Interestingly, there was less marrow toxicity and a decrease in the rate of carboplatin hypersensitivity reactions, which suggests that this drug combination may allow for a longer duration of platinum-based treatment. To examine the combination of carboplatin with PLD vs single-agent carboplatin, Markman et al32 entered 61 patients into a phase III study prior to closure for insufficient accrual. The study initially reported improvement in outcome associated with the combination regimen. Longer follow-up continued to show an improvement in PFS (median: 12 vs 8 months; P = .02) but not OS, albeit limited in its small sample size. The lower incidence of platinum-induced hypersensitivity reactions when combination treatment is administered with PLD was also identified in this study.32

Whereas combination treatment with a platinum doublet is frequently used for recurrent platinum-sensitive patients, especially those with a prolonged disease-free interval, numerous agents are available that can be used as single-agent therapy. Gemcitabine, PLD, topotecan, paclitaxel, docetaxel, oral etoposide, and hormonal agents represent some of the single-agent treatment options. Single-agent treatment is currently the preferred approach for platinum-resistant patients or for platinum-sensitive patients who have a short time to recurrence, such as a 6- to 12-month disease-free interval. Also worthy of consideration is the patient’s anticipated tolerability and cumulative toxicity from the front-line therapy in making the individual treatment selection for recurrent disease.

Secondary Cytoreductive Surgery

In the setting of newly diagnosed ovarian cancer, primary cytoreductive surgery to improve survival is generally accepted. In patients with recurrent disease, the role of cytoreductive surgery continues to evolve. Several series have suggested the importance of cytoreductive surgery prior to the initiation of second-line chemotherapy. In a retrospective analysis, Chi et al33 showed a 41-month median OS after secondary optimal cytoreduction for recurrent ovarian cancer. In another study, investigators demonstrated a 61-month median OS with optimal secondary cytoreductive surgery.34 Given the potential for selection bias in these retrospective studies, GOG 213 includes an evaluation of surgery for recurrent disease. This ongoing phase III trial assesses patients with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer. If patients are surgical candidates, they are randomized to either surgery or no surgery. Once debulked, they are further randomized to carboplatin and paclitaxel chemotherapy or carboplatin, paclitaxel, and bevacizumab chemotherapy followed by maintenance bevacizumab. If patients are not surgical candidates, they are randomized to the chemotherapy with or without the antiangiogenic agent. The objective of this trial is to examine the impact of secondary
cytoreductive surgery. In addition, this study examines the role of the antiangiogenic agent bevacizumab with paclitaxel and carboplatin re-treatment. Accrual for this study is ongoing and results are pending.\textsuperscript{35}

**Phase I/II Trials**

Over the past decade an emphasis on understanding the molecular pathways involved in cancer cell growth, metastasis, and the development of chemoresistance has led to the evaluation of numerous drugs to target these pathways. Targeted therapeutic agents are currently being analyzed in clinical trials at single-institution, multi-institutional, and consortium levels. Tissue procurement has been included in many of these trials to evaluate translational endpoints in order to select patients for enrollment and to monitor therapeutic response.

**Antiangiogenic Agents**

Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody that binds and neutralizes all forms of VEGF. The use of bevacizumab in recurrent ovarian cancer has been explored with promising results and response rates of up to 24%.\textsuperscript{36-38} As described above, bevacizumab has been recently investigated with promising results as a component of front-line and maintenance therapy and is currently undergoing evaluation with gemcitabine and carboplatin for platinum-sensitive recurrent disease. VEGF-Trap is a potent angiogenesis inhibitor fusion protein. In a phase II trial using aflibercept, 41% of patients demonstrated stable disease or a partial response to therapy at 14 weeks on the drug.\textsuperscript{39} Rather than neutralizing the VEGF molecule, another therapeutic strategy for antiangiogenic agents is to block the VEGF receptor. This can be accomplished with agents such as sorafenib or sunitinib, which are orally administered, small molecules that block tyrosine kinase activity located in the cytoplasmic domain of VEGF receptor (VEGFR). Some of these small molecules block VEGFR specifically, whereas others, such as sorafenib and sunitinib, block both VEGFR and the platelet-derived growth factor (PDGFR), thought to be involved in later phases of tumor angiogenesis relating to vessel maturation. Numerous protocols evaluating antiangiogenic agents in combination with cytotoxic chemotherapy for recurrent disease are currently open.\textsuperscript{40}

**mTOR Inhibitors**

Dysregulation of mTOR signaling occurs in many tumors and has been found to be activated in gynecologic cancers. Increased AKT/PI3K activity with constitutive downstream activation of the mTOR pathway has been found in ovarian tumor specimens and ovarian cancer cell lines. Inhibition of mTOR by agents such as temsirolimus (CCI-779), everolimus (RAD001), and deforolimus (AP23573) are in clinical trials. GOG 170I, a phase II study for recurrent/persistent ovarian cancers, evaluated the use of temsirolimus in recurrent/persistent ovarian and primary peritoneal cancers. Results were presented at the 2010 meeting of the Society of Gynecologic Oncologists and suggested modest activity of weekly single-agent temsirolimus in persistent or recurrent disease, with 24.1% PFS at ≥ 6 months. Circulating tumor cells were analyzed pre- and post-treatment to identify predictors for therapeutic response.\textsuperscript{41}

**PARP Inhibitors**

Inhibition of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP), a key enzyme in the repair of DNA, may lead to the accumulation of breaks in double-stranded DNA and cell death. Therefore, PARP inhibitors have been developed and are potentially exciting agents in the treatment of ovarian cancer, especially cancers with BRCA1 and BRCA2 mutations. In a sentinel article, a phase I study showed the PARP inhibitor olaparib lacked severe toxic effects of conventional chemotherapy and resulted in objective responses of tumors with BRCA mutations.\textsuperscript{42} An International Collaborative Expertise for BRCA Education and Research through Genetics (ICEBERG) designed two of the key clinical trials in germline mutation carriers. A phase II trial of the oral PARP inhibitor olaparib (AZD2281) is an international, multicenter, single-arm study with treatment consisting of continuous use of oral olaparib in BRCA-mutation ovarian cancer patients. The interim analysis from October 31, 2008, showed clinical benefit in 57.6% of patients at 400 mg twice daily. The use of PARP inhibitors may not be limited to patients with germline mutations in the BRCA gene.\textsuperscript{43-47} One molecular characterization study suggested that more than 50% of patients with high-grade sporadic epithelial ovarian cancer had loss of BRCA function, by either genetic or epigenetic events.\textsuperscript{48} Therefore, a phase II, randomized, double-blind, multicenter study is assessing the efficacy of AZD2281 in the treatment of patients with platinum-sensitive serous ovarian cancer following treatment with two or more platinum-containing regimens.\textsuperscript{49}

**Histone Deacetylase Inhibitors**

Aberrant histone modifications such as hypoacetylation have been associated with malignancy through the transcriptional silencing of tumor suppressor genes. Belinostat is a histone deacetylase inhibitor (HDAC) that can alter the acetylation level of histone and nonhistone proteins. Such epigenetic modulation may sensitize drug-resistant tumor cells to other antineoplastic agents, as suggested in preclinical studies.\textsuperscript{50,51} A phase II study by the GOG (protocol 0126T) is examining the use of belinostat in combination with carboplatin among patients with recurrent or persistent platinum-resistant disease.\textsuperscript{52}

**Chemoprevention**

In addition to exploring treatments for ovarian cancer, several clinical trials are examining preventive agents. Along with parity, oral contraceptive use has consistently

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been associated with a decreased risk of ovarian cancer. GOG 214, an ongoing phase II double-blind randomized trial, is evaluating the effects of levonorgestrel on the ovarian epithelium in women at high risk for ovarian cancer.\textsuperscript{53} The goal of this trial is to develop a pharmacologic prevention strategy. The primary endpoint will evaluate the frequency of apoptosis of ovarian epithelium, and the secondary endpoint will estimate the impact of this drug on proliferation and transforming growth factor-beta expression in ovarian epithelium.

Fenretinide, a synthetic vitamin A analog, was proposed for chemoprevention of ovarian cancer. Fenretinide reduced ovarian carcinoma occurrence during the 5-year intervention period, but the effects disappeared after treatment.\textsuperscript{54}

Quality of Life Studies

As of this printing, 78 studies on quality of life are registered with http://www.clinicaltrials.gov, a service of the US National Institutes of Health. The burden of disease and the effects of ovarian cancer treatment on everyday living have been increasingly recognized. These include issues pertaining to chronic pain, lymphedema, neuropathy, fatigue, and sexual function, to name a few. Many investigators are now studying both the temporary and sustained effects of ovarian cancer and its associated treatments. Clinical trials are increasingly including quality of life components in trial designs in efforts to both prolong and improve the quality of life among ovarian cancer patients.

Conclusions

Clinical trials in ovarian cancer represent a rich area of investigation. Study design is targeted to address the optimal treatment and side effect profile at various points in the disease course. Increasingly, translational endpoints and quality of life considerations are included as components of these trials. Clinical trials open today build on the results of prior studies in order to optimize the outcomes for women with this challenging disease. Whereas this manuscript focuses on clinical trials pertaining to the management of epithelial ovarian cancers, there are only limited studies available for non-epithelial subtypes due to the low frequency of these tumors. The GOG has recently developed a rare tumor working group to provide a dedicated focus and increase the clinical trial effort for these tumors as well.

References


22. ICON7 - A Randomised, Two-Arm, Multi-Centre Gynaecologic Cancer InterGroup Trial of Adding Bevacizumab to Standard Chemotherapy (Carboplatin and Paclitaxel) in Patients With Epithelial Ovarian Cancer.