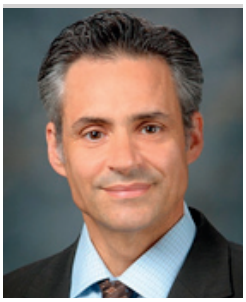
Chapter 11 |

The GOG Foundation, Inc. NRG Rare Tumor Committee





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Introduction

The NRG Rare Tumor Committee was established as a working group in 2005. This initial venture was supported based on the advocacy of David Gershenson, MD, the first group Chair; Ted Trimble, MD, MPH, the Cancer Therapy Evaluation Program's (CTEP) GOG liaison; and Philip DiSaia, MD, Gynecologic Oncology Group (GOG) Group Chair. It subsequently became a full committee based on the group leadership's recognition of the increasing importance of rare gynecologic tumor research.

For example, prior to the establishment of this committee, all ovarian cancer histotypes were generally included in ovarian cancer phase II and III clinical trials. As new information emerged regarding the distinct clinical behaviors and specificity of molecular profiling of rare histologic subtypes, clinical trials were developed considering these unique characteristics.NRG Rare Tumor Committee facilitated a productive pathway to develop more effective therapies, enhance the knowledge base, and improve patient outcomes through hypothesis-driven research. This research has included retrospective cohort, pilot, phase II, randomized phase II, and randomized phase III trials. Additionally, gains in understanding of rare tumor types have been applied to more common tumor types and studied across organ sites.

This research strategy, novel at its inception, was subsequently endorsed during the 2010 Gynecologic Cancer InterGroup (GCIG) International Ovarian Cancer Consensus Conference[1] and the 2011 National Cancer Institute (NCI) Clinical Trials Planning Meeting.[2] Delineation of rare tumor types for study has become the standard.

During the committee's inaugural meeting in July 2005, 15 members were present. The meeting agenda focused on a brainstorming session to begin to formulate a consensus around rare gynecologic tumor research. Dr. Trimble discussed the support of CTEP for the development of clinical trials of rare gynecologic cancers. In addition, the following issues were discussed:

1. There was consensus that, to be successful in this area, GOG would need to commit leadership support and sufficient resources (pathology support, biostatistical support, translational science support, etc.) to conduct the mission.

2. It was likely that the establishment of a Rare Tumor Committee would meet with some resistance within the group as it advocated for additional resources, but those present were optimistic about the ultimate outcome.

3. The group consensus was that patient advocacy groups could be helpful in promoting rare gynecologic cancer research.

4. The group noted that partnering with industry would also be a key factor in the committee's success.

5. Much of the meeting was devoted to defining a "rare gynecologic cancer." There was a consensus that there is no perfect or universal definition. There was, however, a consensus that the group should initially focus on a relatively small number of specific types.

6. The group agreed that translational objectives should be included in virtually all the committee's trials.

7. The group agreed that there was an opportunity to partner with the GCIG, other groups in the NCTN, and foreign groups to conduct intergroup and international studies to maximize patient accrual.

The Rare Tumor Committee reviewed a comprehensive list of rare gynecologic malignancies and through a consensus approach with the other committees, agreed to focus primarily on the following tumor types:

- Ovarian sex cord-stromal tumors
- Malignant ovarian germ cell tumors
- Mucinous ovarian cancers
- Clear cell ovarian cancers
- Low-grade serous ovarian cancers (LGSOC)
- Carcinosarcoma of the ovary
- Small cell carcinomas of the ovary and cervix
- Mucosal melanoma of the lower genital tract

Dr. Gershenson served as the Chair and Allan Covens, MD, served as the Co-Chair from 2005-2017. Dr. Covens has served as the Chair and Jubilee Brown, MD, has served as the Co-Chair from 2018 to present. The committee roster has grown to include representatives from pathology, radiation oncology, medical oncology, biostatistics and advocacy.

Significant Accomplishments
Significant accomplishments of the NRG Rare Tumor Committee include:

1. Establishment of a working group that then transitioned to a full committee focused on rare gynecologic malignancies.

2. Development of hypothesis-driven research in rare tumors with novel agents, innovative statistical design, and translational research components (GOG 0239, GOG 0241, GOG 0251, GOG 0254, GOG 0264, GOG 0268, GOG 0281), presented and national and international meetings and published in highly ranked journals.

3. Development of international collaborations to enhance patient accrual for rare tumor studies (GOG 0241, GOG 0268, GOG 0281, AGCT1531, GY019, and A091903).

4. Activation of the RFP mechanism for protocol concept submission in July 2008.

5. Addition of patient advocates to the committee.

6. Establishing protocols for rare tumors, which has resulted in an evolution of excluding them from eligibility for broad phase II and III trials that have historically included all tumor subtypes, thereby potentially eliminating exposure to ineffective therapy.

7. Engagement with national and international groups committed to rare tumors, with establishment of international guidelines and a mobile app for best practice surrounding rare tumors.

8. Two educational symposia in conjunction with the summer NRG meetings. “Clinical Trials For Rare Gynecologic Cancers” (2014), and “Not So Rare Ovarian Tumors” (2017).

Mentorship
The Rare Tumor Committee includes a combination of both senior and junior investigators. On many of the trials, senior team members have, or are mentoring junior members. Examples include GOG 0239 (Drs. Gershenson/Birrer and Farley), GOG 0241 (Drs. Gershenson and Frumovitz), GOG 0251 (Drs. Gershenson and Brown), GOG 0264 (Drs. Gershenson and Brown), GOG 0268 (Drs. Birrer/Gershenson and Farley), GOG 0281 (Drs. Gershenson and Gourley/Farley), GOG 0283 (Drs. Aghajanian and Hyman), GY001 (Drs. Gershenson and Farley), GY016 (Drs. Coleman and Gien), and GY019 (Drs. Gershenson and Fader). In addition to the above, and as part of NRG’s commitment to new investigator initiatives, the Rare Tumor Committee has supported new investigator concepts and involvement in the process.

Clinical Trials of the Rare Tumor Committee
Since 2007, the Rare Tumor Committee has stewarded over 17 clinical trials, with more than a dozen activated and one (GOG 187) transferred in from the Ovarian Committee. Integration with GOG-Partners (detailed in Chapter 2), has brought a broader array of clinical trial opportunites as well as strategic development leverage, capitalizing on preclinical and early clinical trial observations.

The NRG Rare Tumor Committee portfolio includes:

- **GOG 0187:** “A phase II study of paclitaxel for ovarian

stromal tumors as second-line therapy."[3]

At the time that this trial was conceived, information from both retrospective and prospective studies employing the most common chemotherapy regimens (cisplatin, doxorubicin, and cyclophosphamide; vinblastine, bleomycin, and cisplatin; or bleomycin, etoposide, and cisplatin) indicated substantial toxicity and limited durable activity.[4-7] Thus, in the search for novel agents with enhanced activity, the study of paclitaxel was a reasonable strategy. This trial was opened to patient entry in 2000. It was modified to include only patients with recurrent disease undergoing second-line therapy based on retrospective data underscoring the role of platinu.[8] Enrolling only patients with recurrent disease, the GOG 187 trial closed to patient entry in 2013. The primary objective was to estimate the probability of clinical response and toxicity of paclitaxel as second-line chemotherapy in patients with measurable disease. Of the 31 patients enrolled in this study, there was one complete response (3%) and eight partial responses (26%). Median progression-free survival was 10 months, and the median overall survival was 73.6 months. Grade 3 or 4 myelosuppression occurred in 39% of patients. The authors concluded that paclitaxel should not be evaluated further as a single agent in recurrent malignant ovarian stromal tumors with measurable disease. Additionally, the translational component demonstrated that pretreatment inhibin levels were not a reliable tumor marker.[3]

- **GOG 0239:** "A phase II trial of AZD6244 (NSC# 748727, IND# 77782) in women with recurrent low-grade serous carcinoma of the ovary or peritoneum."[9]

  Low-grade serous carcinoma of the ovary or peritoneum may arise de novo or following an original diagnosis of serous tumor of low malignant potential and represent an entity distinct from high-grade serous ovarian carcinoma. Women with LGSOC are diagnosed at a younger age on average and have a significantly longer overall survival than women with high-grade serous carcinom.[10] It is relatively not as sensitive to chemotherapy as high-grade ovarian subtypes, and hormonal therapy has demonstrated activity in approximately 10% of patients with recurrent disease.[11,12] However, with either chemotherapy or hormonal therapy, the stable disease rate is over 60%. Nevertheless, a continued search for novel agents is of great importance. Because the MAPK pathway appears to be prominent in the pathogenesis of low-grade serous carcinomas, with KRAS mutations in the range of 30-40% and BRAF mutations of about 5%, investigators have focused on trials using MEK inhibitors for this subtype.[13, 14]

  GOG 0239 was opened to patient entry in 2007 and closed to new patient entry in 2009.9The primary objective of this trial was objective tumor response and toxicity. Fifty-two patients were enrolled in this study and were treated with selumetinib 50 mg twice daily, orally, until progression. Eight (15%) patients had an objective response to treatment, with one complete response and seven partial responses. However, an additional 34 (65%) patients had stable disease. Grade 4 toxicities were cardiac (one), pain (one), and pulmonary events (one). Grade 3 toxicities that occurred in more than one patient included gastrointestinal (13), dermatological (9), metabolic (7), fatigue (6), anemia (four), pain (four), constitutional (three), and cardiac events (two). The median progression-free survival was 11.0 months, and median overall survival had not been reached at the time of the publication. Formalin-fixed, paraffin-embedded tissue with sufficient DNA was available for mutational analyses for BRAF and KRAS in 34 patients. Two (6%) had BRAF mutations, and 14 (41%) had KRAS mutations. Unfortunately, there was no correlation between response and mutational status. The authors concluded that selumetinib demonstrated activity in recurrent low-grade serous carcinoma of the ovary and that additional study of inhibitors of the MAPK pathway were warranted. The findings of this study have led to a replacement study—GOG 0281 (see below).

- **GOG 0241:** "A GCIG InterGroup multicenter phase III trial of open label carboplatin and paclitaxel +/- NCI-supplied agent: bevacizumab (NSC #704865, IND# 113912) compared with oxaliplatin and capecitabine +/- bevacizumab as first-line chemotherapy in patients with mucinous epithelial ovarian or fallopian tube cancer (mEOC)." [15]

  Women with advanced stage mucinous carcinomas of the ovary have a much shorter progression-free and overall survival than those with advanced stage serous carcinomas and are more likely to fail adjuvant platinum-based chemotherapy regimens.[16, 17] In addition to differences in clinical behavior, laboratory data support molecular differences between the different epithelial subtypes of ovarian cancer18. For this trial, the investigators hypothesized that a colorectal cancer-type therapy may offer a better outcome compared to the standard for patients with

mucinous carcinomas of the ovary. Thus, this trial was designed to determine if oxaliplatin and capecitabine +/- bevacizumab improves progression-free and overall survival when compared to carboplatin and paclitaxel +/- bevacizumab in women with advanced stage mucinous ovarian cancer.

This was an international, collaborative, randomized trial led by investigators in the United Kingdom partnering with the GOG/NRG. Central pathology review was not required. The primary objective of this trial was: 1) to determine if capecitabine and oxaliplatin reduces the death rate compared to carboplatin and paclitaxel; and 2) to determine if bevacizumab reduces the death rate compared to no bevacizumab. Based on slow accrual on both continents, the trial was stopped after 50 patients were accrued. Median follow-up was 59 months. OS hazard ratios (HR) for the two main comparisons were: 0.78 (p = 0.48) for oxaliplatin and capecitabine vs. paclitaxel and carboplatin, each with/without bevacizumab; and 1.04 (p = 0.92) for bevacizumab vs. no bevacizumab. Corresponding PFS HRs were: 0.84 and 0.80. Although prospective central pathology review was not performed, a retrospective central pathology review revealed that the majority of accrued patients (55%) of patients with available material had metastatic mucinous carcinoma of the ovary; 45% (18/40) of evaluable patients had confirmed primary mEOC. Among these, OS HR for Oxal-Cape vs. Pac-Carbo was 0.36 (p = 0.14); PFS HR = 0.62 (p = 0.40).

This trial highlighted many learning points in the study of rare tumors, as logistical challenges lead to early closure of the trial. Since local histopathological diagnosis of such rare tumor types was problematic and misdiagnosis was frequent, the authors suggest that rare cancer trials should have a centralized pathology review performed before treatment. Drug acquisition was difficult in some locations, as some drugs prescribed were outside their labelled indication. Keeping the trials open locally was also challenging, as these trials may not enroll a large number of patients in any one site, so enthusiasm for funding at a local level was problematic in some locations. This led to the recognition that cooperative groups need to openly support rare tumor trials and support exemptions for high accruals for these trials. While no definitive recommendations can be made based on the patient outcomes in this trial, valuable lessons were learned, and it is clear that rare cancer trials should include centralized pathology review before treatment.[15]

- **GOG 0251:** "A phase II trial of NCI-supplied agent: bevacizumab (NSC# 704865, IND# 7921) for recurrent sex cord-stromal tumors of the ovary."[19]

  Ovarian sex cord-stromal tumors are rare, accounting for only 5-7% of all ovarian malignancies. Surgery remains the cornerstone of initial treatment. However, effective systemic treatment remains relatively ineffective.[3-6,19] Although both cytotoxic chemotherapy and hormonal therapy have modest activity, a search for more effective treatments is definitely warranted. Angiogenesis appears to be an important mechanism in the development of sex cord-stromal tumors of the ovary, and bevacizumab was anecdotally seen to have activity.[20,21] Thus, this study proposed to evaluate bevacizumab as a biologic agent in patients with this rare subtype.

  The trial opened to patient entry in 2008 and closed to patient entry in 2011. The primary objective was to estimate the frequency of objective response in patients with recurrent ovarian sex cord-stromal tumors. Thirty-six patients were enrolled in this study. Six patients (16.7%) had partial response, 28 patients (77.8%) had stable disease, and two (5.6%) had progressive disease. The median progression-free survival was 9.3 months. The authors concluded that bevacizumab has activity in the treatment of recurrent sex cord-stromal tumors of the ovary with acceptable toxicity.

- **GOG 0254:** "A phase II evaluation of SU11248 (Sunitinib Malate) in the treatment of persistent or recurrent clear cell ovarian carcinoma."[22]

  Patients with advanced stage or recurrent clear cell carcinoma appear to have a worse prognosis than those with serous carcinomas.[17,23] Ovarian clear cell carcinomas have molecular similarities to renal cell carcinoma, with angiogenesis playing a central role in both tumor types.[23-27] Thus, novel agents that are active in metastatic renal cell carcinoma may have activity in ovarian clear cell carcinoma. This trial was opened to patient entry in 2010 and closed to patient entry in 2013. The primary objective of this trial was to evaluate the response rate and toxicity of sunitinib malate, a highly potent, selective tyrosine kinase inhibitor, in patients with persistent or recurrent clear cell ovarian carcinoma. Of the 30 evaluable patients, five (16.7%) patients had PFS ≥6 months (90% CI: 6.8%-31.9%). Two (6.7%) patients had a partial or complete response (90% CI: 1.2%-19.5%). The median PFS was 2.7 months. The median overall survival was

12.8 months. The most common grade 3 adverse events were fatigue (4), hypertension (4), neutropenia (4), anemia (3), abdominal pain (3), and leukopenia (3). Grade 4-5 adverse events included: thrombocytopenia (5), anemia (2), acute kidney Injury (1), stroke (1), and allergic reaction (1). This was a negative trial, and sunitinib did not meet the threshold to be considered and active drug so will not be studied further in clear cell carcinomas of the ovary.[22]

- **GOG 0264:** "A randomized phase II trial of paclitaxel and carboplatin vs. bleomycin, etoposide, and cisplatin for newly diagnosed advanced stage and recurrent chemonaive sex cord-stromal tumors of the ovary."[28]

  The optimal first-line chemotherapy regimen for ovarian sex cord-stromal tumors is unknown. Although BEP (bleomycin, etoposide, and cisplatin) has been the most common regimen, it is associated with considerable toxicity and a significant risk of recurrence.[6,7,9] More recently, taxane-based therapy has shown activity in this tumor type.[8,29] This trial was conducted to determine the PFS of paclitaxel and carboplatin (PC) versus BEP for treatment of newly diagnosed Stage IIA-IV or recurrent chemo-naive ovarian sex cord-stromal tumors. This was a phase II, open-label, non-inferiority trial where patients were randomized to six cycles of PC (6 cycles P 175 mg/m2 and C AUC=6 IV every three weeks) versus four cycles of BEP (four cycles B 20 units/m2 IV push day 1, E 75 mg/m2 IV days 1-5, and P 20 mg/m2 IV days 1-5 every three weeks). This trial was opened to patient entry in 2010. The initial targeted patient accrual was 128 patients, but at the predetermined interim futility analysis, 63 patients were accrued (31 received PC and 32 received BEP) and the trial was closed early for futility of PC. The median age was 48 years; 87% had granulosa cell tumors and 37% had measurable disease. The futility analysis was supported by 21/16 PFS events on the PC/BEP arms respectively, with an estimated HR=1.12 [95% CI: 0.58 to 2.16]. Median PFS was 27.7 months [7.4 to 41.0] for PC and 19.7 months for BEP [95% CI: 10.4–52.7]. PC patients had fewer grade 3 or higher adverse events (PC 77% vs BEP 90%). Differences included infections (0 vs. 10%), low neutrophil count (65% vs. 84%), and low WBC (22 vs. 40%). One death not otherwise specified occurred on the PC arm. Compared to BEP, PC failed to improve PFS in ovarian SCSTs. PC showed a more favorable side effect profile. This trial will likely establish the standard of care for upfront adjuvant therapy for patients with sex cord-stromal ovarian tumors.

- **GOG 0268:** "A phase II evaluation of Temsirolimus (CCI-779) (NSC# 683864, IND# 61010) in combination with carboplatin and paclitaxel followed by Temsirolimus consolidation as first-line therapy in the treatment of clear cell carcinoma of the ovary."[30]

  Most studies have shown that patients with advanced stage clear cell carcinoma of the ovary have a worse prognosis than those with advanced stage serous carcinomas.[23,24,30] It is widely thought that this difference is attributable to the lack of effectiveness of conventional chemotherapy. Over the past few years, multiple investigations have demonstrated that approximately 50% of ovarian clear cell carcinomas may have dysregulation of the PI3K/AKT/mTOR pathway.[26,27] Based on this preclinical information, it is theorized that mTOR inhibitors may have activity in clear cell carcinomas of the ovary.[31] Therefore, temsirolimus, an mTOR inhibitor, is given concomitantly with chemotherapy and then as single-agent maintenance therapy. This study was opened to patient entry in 2010 and closed in 2014. This is an international trial, led by the NRG and enrolled in the United States, Japan, and Korea.

  In total, 90 patients were accrued; 45 were accrued in the US and Korea, and 45 were accrued in Japan. The primary objective of this trial is to assess the activity of the study regimen as measured by the proportion of patients who are alive and progression-free for at least 12 months after study entry. In addition, this study compares the outcome of patients from the US and Japan to identify potential differences in these cohorts of patients. In patients with measurable disease, in the US/Korea, 31% (n = 4) and 23% (n = 3) had complete or partial responses, respectively, while in Japan, 6% (n = 1) and 65% (n = 11) did. Median PFS (OS) was 11 (23) months for US/Korea, and 12 (26) months for Japan. Most (85%) patients (88% US/Korea, 82% Japan) were optimally debulked. In the US, 0% of sub optimally debulked patients had PFS > 12 months, and 49% of optimal patients did; in Japan, these were 25% and 59%. In neither the US/Korea nor Japan was the 12-month PFS significantly ($p > 0.05$) better than historical controls. There was no statistically significant difference in PFS or OS between US/Korea and Japan. Carboplatin/paclitaxel + temsirolimus was well tolerated. Optimally debulked patients benefited most, with 54% having a PFS > 12 months. When compared to historical controls this regimen did not statistically significantly increase PFS at 12 months.[30] While the chemotherapy combination will likely not be studied

further, this trial demonstrated the ability of the NRG Oncology Cooperative Group to accrue rapidly to rare tumor trials through international partnership.

- **GY001:** "A Phase II Trial of Cabozantinib in Women with Recurrent Clear Cell Carcinoma of the Ovary, Fallopian Tube, or Peritoneum."[32]

  Based on the distinct histologic characteristics and the importance of the MET receptor in the regulation of clear cell carcinomas, cabozantanib was selected for study, as it is an orally bioavailable multitargeted tyrosine kinase inhibitor whose primary targets includes MET.[24, 26, 27, 33] Primary endpoints were six-month progression-free survival (PFS) and complete or partial tumor response. Thirteen patients were accrued over 19 months. No objective tumor responses were seen. Three (23% [95% CI: 5%, 54%]) of 13 patients had PFS ≥6 months, including one patient who received cabozantinib for 23 cycles and was still on treatment as of the data cut-off date. Median PFS and OS were 3.6 and 8.1 months, respectively. There was one patient with a grade 5 event: a thromboembolic event considered possibly related to study therapy; patient's cause of death was determined to be due to disease and protocol treatment. Four other patients had thromboembolic events (two grade 3 and one each grade 1 and grade 2). Other grade 3 or higher events reported in two or more patients were nausea, vomiting, fatigue, dyspnea, and dehydration. Based on this minimal activity, this was a negative study.[32]

- **GOG 0283:** "A Phase II Trial of DCTD-Sponsored Dasatinib (NSC #732517, IND #120636) in Recurrent/Persistent Ovary, Fallopian Tube, Primary Peritoneal, and Endometrial Clear Cell Carcinoma Characterized for the Retention or Loss of BAF250a Expression."

  Based on data suggesting that clear cell carcinomas have an ARID1a mutation as a key driver in tumorigenesis, and that the tyrosine kinase inhibitor dasatinib causes a synthetic lethal event with ARID1a mutated clear cell carcinoma cells,[34] dasatinib was chosen for study in patients with gynecologic clear cell carcinomas, including ovarian, peritoneal, and endometrial. While there was some discussion about enriching the population by selecting only patients with loss of BRG-associated factor 250a (BAF250a) expression, ultimately patients were stratified by presence or loss of BAF250a expression.

  The primary objective was to assess the clinical activity of dasatinib in patients with recurrent or persistent ovarian, fallopian tube, primary peritoneal, and endometrial clear cell carcinoma using objective tumor response (complete and partial): In patients without loss of BRG-associated factor 250a (BAF250a) expression and in patients with loss of BAF250a expression. The study opened on February 3, 2014, and accrued 35 (28 treated and eligible) of a planned 62 patients. The study was closed on August 10, 2016, after evaluation of the stage 1 data. Just one patient (3.6%) had an objective response and serious adverse events were observed in 57% of patients. Translational data are pending.

- **GOG 281:** "A Randomized Phase II/III Study to Assess the Efficacy of Trametinib (GSK1120212) in Patients with Recurrent or Progressive Low-grade Serous Ovarian Cancer or Primary Peritoneal Cancer."[35]

  This is a follow-up study to GOG 0239, which evaluated selumetinib in LGSOC. This phase II/III trial uses trametinib, an oral, non-ATP competitive, small molecule inhibitor of MEK 1/2, and randomizes patients between standard of care (letrozole, tamoxifen, paclitaxel, pegylated liposomal doxorubicin, or topotecan) and trametinib. In addition, patients on standard of care who progress are permitted to crossover to the investigational agent.

  The primary objective is progression-free survival, and the study includes several translational endpoints. The study opened in February 2014 and closed in April 2019 after meeting its target accrual of 250 patients. Results were presented at the European Society of Medical Oncology in 2019. Of 260 enrolled patients with a median follow-up of 31.4 months, PFS was significantly improved for patients receiving trametinib compared to patients receiving standard of care therapy (median, 13.0 vs 7.2 mo; HR 0.48; 95% CI, 0.36-0.64; P < .0001). Overall response rate was 26.2% for trametinib vs 6.2% for patients receiving standard of care therapy (OR 5.4; 95% CI, 2.39-12.21; P< .0001); duration of response was significantly better (median, 13.63 mo; 95% CI, 8.08-18.76; vs 5.88 mo; 95% CI, 2.76-12.19); and median OS was 37.0 mo (95% CI, 30.3-NE) vs 29.2 mo (95% CI, 23.5-51.6) (HR 0.75; 95% CI, 0.51-1.11). The authors concluded that compared to therapies previously considered standard of care, trametinib was associated with significantly improved PFS and ORR in women with recurrent LGSOC35. This agent is listed in the National Comprehensive Cancer Network recommendations as an option for low grade serous ovarian cancer.

- **GY019:** "A Randomized Phase III, Two-Arm Trial of Paclitaxel/Carboplatin/Maintenance Letrozole Versus Letrozole Monotherapy in Patients with Stage II-IV, Primary Low-Grade Serous Carcinoma of the Ovary or Peritoneum."

  Patients with low-grade serous carcinoma of the ovary do not respond to cytotoxic chemotherapy as well as patients with high grade serous carcinoma of the ovary.[36] Based upon retrospective data suggesting efficacy with anti-estrogen therapy, this study is a defining trial that seeks to establish the standard of care - chemotherapy plus maintenance letrozole versus letrozole therapy only- in patients with low grade serous carcinoma. This study opened in 2020 with international participation and has an enrollment goal of 450.

- **AGCT1531:** "A Phase 3 Study of Active Surveillance for Low Risk and a Randomized Trial of Carboplatin vs. Cisplatin for Standard Risk Pediatric and Adult Patients with Germ Cell Tumors."

  This trial, conducted in conjunction with the Children's Oncology Group, seeks to: 1) establish the utility of observation in (minimally staged) stage I patients with immature teratoma and low risk germ cell tumors; and 2) evaluate the efficacy and toxicity of BEP vs BEC. This trial opened in 2017 and is currently enrolling with a projected completion date of 2027. The projected sample size is 2,059 patients. Eligible patients need to be enrolled within six weeks of biopsy or surgery. Adult low-risk patients have stage IA or IB grade 2 or 3 pure immature teratoma of the ovary (< 5% of microscopic yolk sac tumor), mixed immature and mature teratoma with no pathological evidence of mixed germ cell tumor, AFP <1000 ng/mL, age <50; or have Stage IA or IB ovarian or extragonadal yolk sac tumor, embryonal carcinoma, or choriocarcinoma (pure or mixed) and age <50. These low-risk patients are observed and monitored according to close history, physical, laboratory (tumor markers), and imaging parameters. Adult standard-risk patients have Stage IC-III ovarian or extragonadal yolk sac tumor, embryonal carcinoma, or choriocarcinoma (pure or mixed) at age > 11 and < 25 years. Patients are randomized to three cycles of bleomycin, etoposide, and cisplatin versus three cycles of bleomycin, etoposide, and carboplatin.

- **E2607:** "A phase II trial of Dasatinib in KIT-positive patients with unresectable locally advanced or stage IV mucosal acral and vulvovaginal melanomas" (Leitao).

  This trial is an ECOG study with an NRG cohort of patients with vulvovaginal melanoma. This study opened in May 2009 and completed accrual in December 2020. Results are pending.

- **GY016:** "A Phase II Study of MK-3475 (Pembrolizumab) (NSC #776864) + Epacadostat (NSC #766086) in Recurrent Clear Cell Carcinoma of the Ovary."

  This was a single-arm two-stage phase II study evaluating the combination of pembrolizumab 200 mg IV every three weeks and IDO-1 inhibitor, epacadostat, 100 mg PO twice a day (cycle=21 days) in patients with recurrent or metastatic clear cell carcinoma of the ovary. Drug regimen was to be given until disease progression or adverse effects prohibiting further treatment. The primary endpoint was complete or partial objective tumor response within seven months of study entry. Secondary endpoints included toxicity, progression-free survival, and overall survival. The targeted accrual was 23 patients.

  Rapid study accrual exceeded the expected number of patients per month and was suspended after reaching the first stage (14 patients) to allow the first stage data to mature. Data from the first stage accrual were recently presented [ref Gien, IGCS 2022]. Median age was 65 (44-89), 10 (71.4%) had ≥ 2 prior regimens. ORR was 21% (95% CI 5-51%) within 7 months of study entry with 3 partial responses, 4 had stable disease for disease control rate of 50%. Median PFS was 4.8 months (95% CI: 1.9-9.6), OS 18.9 months (95% CI: 1.9-NR). Most common grade ≥ 3 adverse events reported were metabolism and GI related. During this accrual pause, preclinical and clinical data emerged to support a higher dose of epacadostat. However, despite achieving a minimum number of tumor responses required to advance to the second stage, the study was closed given the industry's decision to not further develop this combination.

- **A091903:** "A Randomized Phase II Trial Of Adjuvant Nivolumab With Or Without Cabozantinib In Patients With Mucosal Melanoma."

  A member of the NRG Rare Tumour Cmte (Vicus) was instrumental in the conception and design of this study in collaboration with members from Alliance. The study is being led by Alliance and is pending final approval from NCI. This study includes a randomized cohort of patients with R0/R1 resection who will be

randomized to Nivolumab with or without Cabozantinib (N=78). Stratification factors include: disease site, nodal status, PDL-1 status and adjuvant radiation. There will also be an observational cohort of patients with unresectable or metastatic disease who will be treated with combination Nivolumab and Cabozantinib (N=21). The study will include multiple disease sites (H&N, GYN, GI, GU) and will be a collaboration between multiple collaborative groups with a high international interest.

- **GOG-3026:** "Phase II trial of letrozole + Ribociclib for women with recurrent low-grade serous carcinoma." (Slomovitz) GOG Partners

  The efficacy of endocrine therapy in patients with low grade serous ovarian cancer has been well documented. Emerging evidence in other endocrine-sensitive tumors such as estrogen receptor positive breast cancer has demonstrated synergistic activity of endocrine therapy combined with cell cycle kinase inhibitors, particularly CDK4 and CDK6. In light of the many homologies between low-grade serous ovarian cancer and ER-positive luminal breast cancer, there is strong rationale to study this combination in low grade serous ovarian cancer. The trial enrolled 49 patients and data is maturing. The primary endpoint is objective response.

- **GOG 3051:** "A Study Evaluating the Efficacy and Safety of Biomarker-Driven Therapies in Patients With Persistent or Recurrent Rare Epithelial Ovarian Tumors 'The BOUQUET Trial.'"

  This is a phase II, open-label, multicenter platform study evaluating the efficacy and safety of biomarker-driven therapies in patients with persistent or recurrent ovarian tumors utilizes a platform design with four arms of therapy guided by molecular profiling results. This is a collaborative trial with GINECO as the international lead and with GOG-Partners as the domestic lead. Patients must have histologically confirmed, non-high-grade serous, non-high-grade endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer (i.e., low-grade serous ovarian carcinoma, clear cell carcinoma, mucinous carcinoma, carcinosarcoma, undifferentiated carcinoma, seromucinous carcinoma, malignant Brenner tumors, Grades 1 or 2 endometrioid carcinoma, or small cell carcinoma of the ovary-hypercalcemic type. Disease must not be amenable to curative surgery. The trial is designed to roll in new arms based on molecular profiling. The initial design included four arms:

  - *Arm 1:* patients with PTEN loss-of-function alterations and/or PIK3CA- or AKT1- activating mutations receive ipatasertib 400 mg orally once daily days 1-21 + paclitaxel 80 mg/m2 IV days 1, 8, and 15 of each 28-day cycle.

  - *Arm 2:* patients with BRAF-, KRAS-, and NRAS-activating mutations and/or NF1 loss-of-function alterations receive cobimetinib 60 mg orally daily days 1-21 of each 28-day cycle.

  - *Arm 3:* ERBB2 amplification and/or mutations receive trastuzumab emtansine 3.6 mg/kg IV on day 1 of each 21-day cycle.

  - *Arm 4:* non-matched patients receive atezolizumab 1200 mg IV day 1 + bevacizumab 15 mg/mg IV day 1 of each 21-day cycle.

  The primary endpoint is confirmed objective response rate. Secondary outcome measures include duration of response, disease control rate, progression free survival, and overall survival. Each of these arms have completed their enrollment and four new arms are planned.

Typically, the Rare Tumor Committee submits focused requests for proposals to the NRG Oncology membership prior to each meeting based on the areas of need and opportunity. These are informed by preclinical data, advances in the field, and novel drug availability.

Future Directions

By providing a venue for focused interest, the Rare Tumor Committee has maintained a positive trajectory and has helped to change the way that clinical trials are performed in rare gynecologic tumors since its inception. The plan is to continue, informed by preclinical data in conjunction with molecular testing and novel drug design. While several of the Rare Tumor Committee's trials have transformed the practice of gynecologic oncology, the future remains optimistic for continuing to make a difference for patients with rare gynecologic tumors. Smart adaptive trial design to minimize the number of patients to answer a question, molecular profiling, improved understanding of targeted therapy, and innovative models of drug design should aid our ability to effect improvement. A limiting factor in obtaining national funding and approval has been the lack of preclinical data for rare tumors. The Rare Tumor Committee is working on strategies to facilitate this, including brainstorming ses-

sion with stakeholders, to include partnerships with basic and translational scientists, and the pharmaceutical industry to improve and expedite the above process.

Future plans of the Rare Tumor Committee include the following:

1. Continuing to build on the foundation of early studies by conducting a series of trials for the most relevant tumor types.

2. Continuing to advocate and enhance awareness of the nature of rare tumor types.

3. Capitalizing on new discoveries of the molecular biology and clinical behavior of rare tumor types to drive the research agenda.

4. Continuing to utilize the RFP mechanism to vet new rare tumor concepts.

5. Developing a robust collaboration with basic and translational research teams, establishing small working groups of clinical researchers and basic and translational scientists to streamline trial design.

6. Establishing a robust, well-annotated rare tumor bank within the NRG Oncology infrastructure.

7. Continuing international collaborations through the Gynecologic Cancer InterGroup and other international organizations.

8. Continuing to explore innovative trial designs and statistical analyses to maximize information from the fewest patients possible.

9. Exploiting molecular profiling and the platform trial design to achieve the most information from the fewest patients, identifying patients with similar rare tumor characteristics beyond light microscopy and answering multiple research questions at once.

10. Mentoring young investigators and cultivating their passion for rare tumor work.

11. Optimizing the use of ancillary studies of rare gynecologic tumors.

The future is bright for rare tumor study, and NRG Oncology is at the forefront of this work.

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