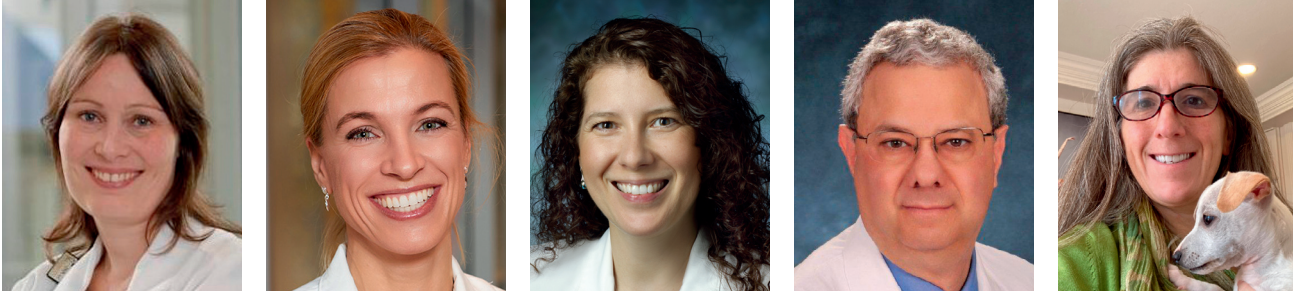


The GOG Foundation, Inc. Developmental Therapeutics Committee Phase I & Phase II Studies



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Abstract

The Gynecologic Oncology Group (GOG) Developmental Therapeutics Committee (DTC) is responsible for phase I and single-arm phase II evaluation of novel therapies in women with gynecologic cancers in collaboration with the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) and the pharmaceutical industry. The Phase I Subcommittee of DTC oversees safety-lead-ins for phase II and III studies and disease-oriented phase I trials in collaboration with GOG Foundation (GOG-F) Site Committees, with an aim toward future randomized phase II and phase III trials. Biomarkers and translational research in phase I and II studies involves a team science approach with active collaboration with members of the Committee on Experimental Medicine (CEM), NRG Oncology Core Laboratory facilities, SPORE/PO1 sites, cancer centers and other funded laboratories. Throughout the protocol development process, the Committee also interacts with the Medical Oncology, Nursing, Data Management, Translational Science, New Investigators and Radiation Oncology Committees. The DTC has a strong mentoring focus; often serving as the entry point for new investigators. Mentoring is accomplished both within and across institutions and is further facilitated by the appointment of DTC liaisons to the NRG New Investigators committee. Junior investigators are matched with experienced investigators/mentors (who function as study co-chairs and senior authors) to advise, counsel and guide through concept and protocol development, safety report reviews, study result evaluation, and ultimately manuscript preparation. The historical evolution of DTC and the key accomplishments that have contributed to clinical and translational science are reviewed.

Introduction

Due to the rarity of each individual type and disease state of gynecologic cancers, few individual centers have the patient resources to conduct independent phase II trials of gynecologic cancers within a reasonable timeframe. Scientific, regulatory, and administrative details require thoughtful prioritization of new concepts. NRG Oncology provides an effective multicenter infrastructure to rapidly prioritize and complete studies.

At this time, clinical trial paradigms are being driven by molecular targeted and immunomodulatory agents. Molecular profiling of tumor genotype, DNA methylation status, mRNA and protein expression patterns, and pharmacogenomics pathways of drug metabolism are being incorporated into clinical trials offering a more personalized approach to treatment for women with these malignancies. The Developmental Therapeutics Committee with its Phase I Subcommittee is tasked with incorporating new treatment paradigms in the phase I/II setting prior to incorporation of these agents into randomized phase II and phase III trials.

History

In 1975, early drug development was performed as pilot studies in the Disease Site Committees. In 1977, J. Tate Thigpen, MD, the then co-Chair of the Protocol Committee, proposed that a pilot study be defined as a phase I or II study and reside under the jurisdiction of the Protocol Committee. Later that year, it was felt that these studies should be under the auspices of the Chemotherapy Committee chaired by George Omura, MD. By 1978, the New Drug Liaison Committee, chaired by Milan Slavik, MD, was formed based on a recommendation from William McGuire, MD, then at CTEP to GOG leadership in-

dicating that GOG should be actively involved in the evaluation of new drugs through phase II trials.

The first phase II study (GOG Protocol 26) was a series of disease-specific sections on a master protocol evaluating the same drug (cisplatin) in multiple disease settings, with activity demonstrated in each of the three major tumor types (ovarian, cervical, and endometrial). A representative of the New Drug Liaison Committee attended NCI Phase I meetings to identify drugs of potential interest for evaluation within the GOG phase II framework. Dr. McGuire transitioned from NCI to a full member institution of GOG, and he joined the New Drug Liaison Committee as co-Chair in January 1982. Other agents and tumor types were added as GOG Protocol 26 became a master phase II template for the entire program. The New Drug Liaison Committee became the New Drug Committee in 1985, chaired by James Arseneau, MD, as it began to evaluate agents in previously untreated patients. Protocols 76 (cervical cancer), 86 (endometrial cancer), and 87 (uterine leiomyosarcomas) were created to provide an opportunity for a subset of institutions to explore new front-line treatments in phase II studies while the remaining sites participated in Group-wide phase III studies. In 1988, Dr. McGuire was charged with development of a Pilot Subcommittee (which changed its name to the Phase I Subcommittee with Phase I Working Group institutions in 1990) of the New Drug Committee with the intent of looking at potential drug combinations and concurrent chemoradiation.

The GOG leadership under Robert Park, MD, formed the Developmental Therapeutics Committee in 1996, to achieve the goals of working alongside both the pharmaceutical industry and the NCI, maximizing opportunities for evaluation of new drugs in gynecologic malignancies. Dr. McGuire was appointed Chair, with primary responsibility for phase I studies and Michael Bookman, MD, Co-Chair, with primary responsibility for phase II studies.

In 1999, Dr. McGuire became co-Chair of the Ovarian Committee and Dr. Bookman transitioned to Chair of DTC. Gini Fleming, MD, was nominated to replace Dr. McGuire as co-Chair of the Phase I Subcommittee and David Spriggs, MD, was subsequently added as a second co-Chair to facilitate integration of translational scientific objectives and provide oversight of the core pharmacokinetic laboratory. Under Dr. Bookman's leadership a system was put in place to evaluate cytotoxic chemotherapies and biologic and/or targeted therapies within distinct queues. The 227 (cervical cancer), 229 (endometrial cancer), 170 (ovarian cancer), 230 (carcinosarcoma) and 231 (leiomyosarcoma) protocols were created to evaluate biologic and/or targeted thera-

pies. A protocol shell was created and maintained for each treatment category/queue. The consistency in eligibility and primary endpoint analysis across studies within a queue allowed for development of an extensive historical controls database.

In view of the increased number and complexity of phase I and II studies, a proposal was made to designate section leaders for each of the major disease sites to work in collaboration with the relevant GOG site committees. During 2002, section leaders were appointed for ovarian cancer (Robert Burger, MD), cervical cancer (Peter Rose, MD), endometrial cancer (R. Scott McMeekin, MD) and gynecologic sarcomas (Gregory Sutton, MD), drawing on experienced GOG members and past study chairs with an active interest in these sites. In conjunction with this organizational change, Dr. Spriggs stepped down as co-chair. In 2004, Dr. Fleming was recruited to serve as co-Chair for the Ovarian Committee, and in 2005, Paula Fracasso, MD, was nominated to serve as co-Chair of DTC and Chair of the Phase I Subcommittee. In 2006, Dr. Bookman stepped down as Chair of DTC and Carol Aghajanian, MD, became chair of DTC and Dr. Fracasso became Chair of the Phase I Subcommittee with Drs. Robert Burger and Charles Kunos as co-Chair of DTC and Phase I Subcommittee, respectively. In addition, Don Dizon, MD; D. Scott McMeekin, MD; Robert Coleman, MD; and Martee Hensley, MD, were the DTC Section Leaders of cervical cancer, endometrial cancer, ovary cancer and gynecologic sarcoma sections, respectively. Jyoti Mayadev, MD, became the Phase I subcommittee co-Chair when Dr. Kunos joined CTEP at the NCI. In 2019, Roisin O'Cearbhaill, MD, took over leadership of DT, with Floor Backes as DT co-Chair, Russell Schilder, MD, and Stephanie Gaillard, MD, as Phase I Co-Chairs and Panos Konstantinopoulos, MD, PhD, became the DT Translational Chair. At present, Dr. Aghajanian remains active as Chair of the Gynecologic Cancer Committee overseeing the disease specific subcommittees. Dr. Aghajanian represents the GOG Foundation at the CTEP Early Drug Development Meetings and as a member of the Investigation Drug Steering Committee (IDSC) of the National Cancer Institute. Dr. O'Cearbhaill represents NRG Oncology in the NCI-ComboMATCH Precision Medicine Cancer Trial successor to the NCI-MATCH study.

Accomplishments

A summary of treatment categories (queues or series) is included in Table 1.

Cervix Cancer

Chemoradiation in cervical cancer (Phase I)

With the demonstration that concurrent platinum-based

chemoradiation can improve survival in patients with locally advanced cervical cancer (LACC), there has been increased interest in developing new treatment regimens. This poses some unique challenges for combined modality trials, such as the monitoring of acute and chronic toxicities, which exceeds the usual scope of phase I trials. In addition, there is no validated phase II paradigm (end-point) for demonstration of efficacy. As such, historically, a promising regimen would need to move from phase I directly to phase III. As such, safety and feasibility are key considerations. The Phase I Subcommittee has focused on combinations of radiation (RT) with cisplatin (CDDP) and paclitaxel (PAC) (9803 and 9804),^{1,2} CDDP and gemcitabine (9912),³ CDDP and topotecan (9913),⁴ and CDDP with cetuximab (9918),⁵ reflecting emerging experience in the management of advanced cervical cancer. These combinations were feasible but did not merit further development (Table 1). The Phase I Subcommittee then studied treatment following standard cisplatin/RT in women with locally advanced disease with a high risk of recurrence. In GOG-9926,⁶ patients were treated with CDDP with concurrent extended field RT followed by 4 cycles of carboplatin and PAC. This regimen was shown to be tolerable and served as the forerunner for the GOG-274 (OUTBACK Trial)⁷ which was reported at the ASCO annual meeting in 2021 as a negative trial.

Incorporation of Cytotoxic Therapy Including PAC, Topotecan, and Other Agents; Practice Changing Advances for Advanced, Recurrent or Persistent Cervical Cancer (76 and 127 series)

The GOG DTC launched a series of trials both in metastatic/recurrent chemotherapy naïve (76 series) as well as in the post chemotherapy, second line setting (127 series). The summary of these trials is outlined in Table 1. Highlights include, GOG-76S,⁸ where PAC was found to have activity in squamous cancer of the cervix (SCC) with an overall response rate (ORR) of 17%. This was followed by GOG-76X,⁹ a phase II evaluation of PAC and CDDP in combination, which had an ORR of 46%. This led to the phase III trial (GOG-169)¹⁰ which compared CDDP with or without PAC, showing CDDP plus PAC was superior to CDDP alone with respect to ORR and progression-free survival (PFS) with sustained quality of life.

Topotecan was established as an active agent in SCC, achieving an ORR of 19% in patients with no prior chemotherapy (GOG-76U)¹¹ and 12.5% in patients with one prior therapy (GOG-127F).¹² This was rapidly translated to a phase III trial (GOG-179)¹³ comparing CDDP +/- topotecan. This was the first randomized phase III trial to demonstrate an OS advantage for combination chemotherapy over CDDP alone in advanced cervical cancer.

On June 14, 2006, the US Food and Drug Administration approved topotecan in combination with CDDP for the treatment of stage IVB, recurrent or persistent cervical cancer based on the results of GOG-179.¹³

Vinorelbine was combined with CDDP in patients in GOG-76Z,¹⁴ an ORR of 30% was achieved. In GOG 127Q,¹⁵ combination CDDP and gemcitabine showed promise with an ORR of 22%.

These studies provided the basis for a four-arm phase III trial (GOG-204)¹⁶ comparing platinum doublets and showing that vinorelbine/CDDP, gemcitabine/CDDP, and topotecan/CDDP were not superior to PAC/CDDP in terms of OS. The trend in ORR, PFS and OS favored PAC/CDDP. Thus, paclitaxel/ cisplatin remains the standard chemotherapy backbone for this disease.

Several exploratory single arm trials (GOG-76GG and 76 HH)^{17,18} evaluated CDDP-based chemotherapy combinations with newer agents in patients with previously untreated advanced/metastatic disease (Table 1) but none moved forward into phase III trials.

In patients with previously treated recurrent or persistent cervical cancer, a series of monotherapy and combination cytotoxins were studied in single arm phase II trials and add to the NCCN listing of potential therapies but none identified a superior regimen in this setting to advance to phase III testing until GOG-3023/innovaTV 204/ENGOT-cx6¹⁹ demonstrated an ORR of 24% (95 % CI 16-33%) or the antibody drug conjugate tisotumab vedotin and resulted in one of the newest FDA regulatory approvals in 2021 for recurrent cervical cancer. The confirmatory randomized phase 3 trial of tisotumab vedotin as compared to investigator choice chemotherapy post paclitaxel and platinum-based therapy is ongoing as GOG 3057/innovaTV 301 (NCT04697628).

Ongoing is GOG 3024/innovaTV 205/ENGOT cx8 (NCT03786081), which is a phase Ib/II trial of tisotumab vedotin in combination with other agents such as immunotherapy, bevacizumab and carboplatin which may lead to earlier use of this novel asset in cervical cancer in the future.

Incorporation of Targeted Therapy in Cervical Cancer (227 series)

Until recently, bevacizumab was the only biologic/targeted therapy to show significant activity in cervical cancer. In GOG-227C,²⁰ bevacizumab resulted in an ORR of 11% with 24% of patients progression-free at six months. These results contributed to the development of GOG-

240,^{21,22} a phase III trial of chemotherapy with and without bevacizumab in stage IVB, recurrent or persistent cervical cancer that showed an OS advantage with the addition of bevacizumab. PAC/CDDP plus bevacizumab is now defined as a standard care option.

Incorporation of Immunotherapy in the Treatment of Cervical Cancer

Several important immunotherapy-based trials were conducted by the phase I Subcommittee. GOG-9929²³ evaluated the use of ipilimumab after cisplatin/RT. The treatment was found to be safe and favorably modulated the tumor microenvironment. GY002²⁴ examined the anti-PD-1 agent, nivolumab, in patients with recurrent or persistent cervical cancer. It had an acceptable safety profile but exhibited only a 4% response rate. In GY017 investigators studied the effect of immune checkpoint inhibition on the tumor microenvironment by directly comparing the impact of a priming dose of atezolizumab followed by concurrent atezolizumab with cisplatin/RT versus concurrent atezolizumab with cisplatin/RT. Data from this study are currently being analyzed and will likely inform subsequent, larger trials.

GOG-265²⁵ investigated an alternative immune approach using the therapeutic vaccine, axalimogene filolisbac (ADXS-HPV), in patients who had progressed following at least one line of therapy for advanced or persistent disease. The ADXS-HPV vaccine is a live, irreversibly attenuated *Listeria monocytogenes* bacterium which secretes a truncated fragment of listeriolysin O fused to the full length E7 protein of HPV-16. This approach culminates in stimulation of HPV specific effector T cells. It was found to be tolerable. The 12-month overall survival of 38% exceeded the protocol specified benchmark but there is no further development planned at this time for this agent in this disease.

Although the monotherapy trial GY002 of nivolumab did not meet expected ORR, development of this class of agents continued through GOG-F through GOG 3016/EMPOWER- Cervical 1/ENGOT-cx9²⁶ which evaluated the PD-1 blocking monoclonal antibody, cemiplimab compared to investigator choice chemotherapy in 2nd line, recurrent cervical cancer and found a significant improvement in overall survival (HR 0.69; 95% CI 0.56-0.84) and ORR was 16.4% as compared to investigator choice of 6.3%. Simultaneous with this accomplishment was the publication of KEYNOTE 826²⁷ which incorporated pembrolizumab with PAC and platinum +/- bevacizumab as front line therapy and demonstrated an OS benefit as well (HR 0.64 (95% CI 0.50 to 0.81; p<0.001).

This movement of immune therapy into the front-line metastatic setting along with the demonstration from GOG 3016 of the dismal ORR for investigator choice chemotherapy increases the urgency of drug development for patients post front line chemotherapy.

Endometrial Cancer

Incorporation of paclitaxel in the treatment of endometrial cancer (86 and 129 series)

PAC was shown to be the most active single agent therapy tested to date in advanced and recurrent/persistent endometrial cancer (EC) with a 36% response rate in patients who are chemotherapy naïve (GOG-86O)²⁸ and a 27% response rate in patients having received one prior therapy (GOG-129C).²⁹ This led to incorporation of PAC into the initial therapy regimen for EC, initially as part of a 3-drug regimen in GOG-177 (paclitaxel, doxorubicin, cisplatin, or TAP)³⁰ and then as a platinum-doublet in GOG-20931 (PAC/carboplatin). PAC/carboplatin is now the standard initial chemotherapy for advanced, recurrent, or persistent EC based on GOG-209.³¹

Incorporation of Targeted Therapy in Endometrial Cancer (229 series)

The GOG established the promise of anti-angiogenesis agents in EC with GOG-229E,³² a phase II trial of bevacizumab in patients with advanced EC and one to two prior lines of therapy. This trial showed an ORR of 14% with 40% of patients surviving progression free for six months or more. Other anti-angiogenic and targeted agents in the 229 series (Table 1) did not show significant single agent activity. A three-arm randomized phase II study of PAC/carbo-platin plus bevacizumab, PAC/carbo-platin plus temsirolimus and ixabepilone/carboplatin plus bevacizumab as initial therapy for advanced/recurrent EC was performed (GOG-86P).^{33,34} This trial built on work within the GOG evaluating anti-angiogenesis agents, taxanes (86O28 and 129C29 – paclitaxel; 129P – ixabepilone) and temsirolimus (248).³⁵ Progression free survival was not significantly improved compared to historical controls from GOG-209, however, OS was increased in the patients who received carboplatin/PAC/bevacizumab compared to (non-contemporaneous) historical controls and should be interpreted with caution. This study was the first larger trial that showed the importance of translational research to predict clinical outcomes and showed that TSC2 mutations could be predictive of response to temsirolimus. One of the few other combination studies (GOG-229O: MEK inhibitor trametinib with AKT inhibitor GSK2141795)³⁶ demonstrated that despite encouraging activity and a previously established RP2D in other disease sites, this combination had high levels of toxicity in EC and insufficient preliminary efficacy at a tolerable

Table 1. Phase I and II Study Queues

Tumor Type	Ph	GOG	Description	Primary Endpoint	Participants
<i>Cervix</i>	II	127	Recurrent or persistent, one prior therapy (in addition to prior cis-RT)	Response	Group-wide
	II	227	Targeted therapy, recurrent or persistent, 1-2 prior therapies (in addition to prior cis-RT)	Response and PFS6	Group-wide
	II	76	Front-line studies of new combinations, no prior therapy (prior concurrent cis-RT allowed)	Response	Limited access (Cervical cancer phase II working group)
	I	(n/a)	Front-line chemoradiation pilots	DLT-MTD Acute and Chronic	Limited access (Phase I working group)
<i>Endometrium</i>	II	86	Randomized phase II, front-line studies of new combinations, no prior chemotherapy	PFS	Group-wide
	II	129	Recurrent or persistent, one prior therapy	Response	Group-wide
	II	229	Targeted therapy, recurrent or persistent, 1-2 prior therapies	Response and PFS6	Group-wide
	I	(n/a)	Studies of new combinations	DLT-MTD Feasibility	Limited access (Phase I working group)
	I	(n/a)	Front-line chemoradiation pilots	DLT-MTD Acute and Chronic	Limited access (Phase I working group)
	<i>Ovarian, Fallopian Tube, Primary Peritoneal</i>	II	126	Platinum-resistant, recurrent or persistent, one prior therapy	Response
II		170	Targeted therapy, recurrent or persistent, 1-2 prior therapies	Response and PFS6	Group-wide
II		186	Randomized phase II, recurrent or persistent, 1-3 prior therapies	PFS	Group-wide
I		(n/a)	Front-line studies of new combinations, no prior therapy	DLT-MTD Feasibility	Limited access (Phase I working group)
I		(n/a)	First platinum-sensitive recurrence, studies of new combinations, 1 prior therapy	DLT-MTD Feasibility	Limited access (Phase I working group)
I		(n/a)	Recurrent or persistent, multiple prior therapies	DLT-MTD	Limited access (Phase I working group)
<i>Uterine Leiomyosarcoma</i>		II	87	No prior therapy	Response
	II	131	Recurrent or persistent, one prior therapy	Response	Group-wide
	II	231	Targeted therapy, recurrent or persistent, 1-2 prior therapies	Response and PFS6	Group-wide

(Table continued on next page)

Table 1. (Continued)

<i>Uterine Carcinosarcoma</i>	II	232	No prior therapy	Response	Group-wide
	II	130	Recurrent or persistent, one prior therapy	Response	Group-wide
	II	230	Targeted therapy, recurrent or persistent, 1-2 prior therapies	Response and PFS6	Group-wide

PFS6 = Percent of patients progression free at 6 months

Notes:

- Published results for each study performed can be reviewed using the GOG Publication Search Engine, which is available through the GOG Partners website at <https://www.gog.org/gog-partners/search-publications/> and the NRG Oncology website at: <https://www.nrgoncology.org/Home/Member-Login> <https://www.nrgoncology.org/Clinical-Trials/Publications>
- The NRG Oncology Phase I Program Procedure Manual can be reviewed on the NRG website at: https://www.nrgoncology.org/Portals/0/Scientific%20Program/NonDisease%20Site%20Committees/DT/NRG%20Oncology%20Phase%20I%20Proc-Manual_v3_02May2022.pdf?ver=LUEWYBCWfTCWJ6ft4rHpw%3d%3d

dose. Other combinations such as in GOG-248³⁵ (randomized phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced EC) also had to be stopped early due to an excess of venous thromboses and no evidence of superior activity. Results from GOG-229J³⁷ (cediranib) showed this oral agent was relatively well tolerated and led to a new control arm for the investigation of new combinations in GY012³⁸ (single-agent olaparib (which was discontinued due to lack of activity), single agent cediranib, the combination of cediranib/olaparib, the combination of olaparib and capivasertib (AKTi), the combination of olaparib and durvalumab and the combination of cediranib and durvalumab in recurrent, persistent, or metastatic EC). Other targeted agents such as PI3KCA inhibitors (copanlisib in NRG-GY008)^{39,40} for patients with hotspot PIK3CA mutations have shown limited activity as a single agent and novel combinations are warranted.

Immunotherapy for Endometrial Cancer

As mentioned above, NRG GY012 has moved combination therapies with immunotherapies into the recurrent treatment setting for endometrial cancer. At the time of this writing, there are multiple, global trials either fully accrued or close to evaluating incorporation of immune checkpoint inhibitors into front line metastatic treatment. These include NRG GY018 (NCT03914612)⁷⁴ and GOG-F trials DUO-E (NCT04269200) and Ruby (NCT03981796). As mentioned earlier, NRG GY020 seeks to add pembrolizumab as adjuvant therapy following radiation for patients with mismatch repair deficient (MMRd) endometrial cancer considered to be high intermediate risk. In

this setting where more patients may have seen immune therapy in the front-line adjuvant or metastatic setting, the need to explore a post IO setting has become more important. NRG GY025(NCT05112601) activated in February 2022 and will evaluate the combination of ipilimumab and nivolumab as compared to nivolumab in patients with recurrent, MMRd endometrial cancer and will allow those with prior immune therapy provided no recurrence was noted during receipt. Similarly, the GOG Foundation study GOG 3038/PODIUM 204 (NCT04463771) is a multi-arm umbrella trial, evaluating the immune checkpoint inhibitor retifanlimab as monotherapy or in combination with other agents among patients with recurrent endometrial cancer who are MSI-Hi, MMRd or POLE, MSS and FGFR 1, 2 or 3 mutated.

Incorporation of Endocrine Therapy in the Treatment of Endometrial Cancer

Endocrine therapy has long been studied within the NRG/GOG (Table 1) starting with GOG 30, 48, 81, 81F and leading into GOG 159, 168 and 180. GOG 153 which evaluated alternating Megace 80mg po bid and tamoxifen 20mg po bid and reported a high ORR (especially among endometroid tumors) was moved into the RPh2 setting as a control arm for GOG 3007. GOG 3007⁴¹ evaluated oral MTOR inhibitor everolimus with aromatase inhibitor letrozole versus tamoxifen/medroxyprogesterone acetate and showed the greatest benefit in chemo-naïve patients with longer progression free survival in patients receiving everolimus/letrozole and similar toxicity. Here, mPFS was 28 months for everolimus/letrozole as compared to 5 months for tamoxifen/medroxyprogesterone

acetate warranting further development.

GY011⁴² was a novel window study investigating the relationship of short-term Depo-Provera (medroxyprogesterone acetate) compared to Depo-Provera with entinostat on the morphologic, biochemical, and molecular changes in primary endometrioid adenocarcinoma of the uterine corpus. This trial enrolled 50 patients in a record time of 4 months, and while the translational (primary) endpoint showed that entinostat had no immediate effect on progesterone receptor expression, the study showed feasibility to conduct window trials within NRG.

Currently, the GOG F is actively enrolling a single arm phase 2 trial of the CDK4/6 inhibitor abemaciclib plus letrozole for the treatment of advanced or recurrent EC (NCT04393285) and actively in startup for a single arm phase 2 of alpelisib (PI3Ki) plus letrozole for PIK3CA-mutated, estrogen receptor positive, recurrent endometrial cancer (NCT05154487).

Radiation for Endometrial Cancer

Based on advances in knowledge from the molecular subtyping studies, GY020 (NCT04214067) opened in February 2020 and is the first study to limit enrollment to a specific molecular subgroup (mismatch repair deficient EC) in an attempt to deliver more targeted and personalized medicine to improve patient outcomes.

Establishing the Standard of Care for Treatment of Carcinosarcomas (232 and 130 series)

Paclitaxel was shown to have single agent activity ORR of 18% in patients with recurrent carcinosarcoma who had received one prior therapy in GOG-130B.⁴³ The combination of PAC and carboplatin in patients with chemotherapy naïve advanced or recurrent carcinosarcoma had a high level of activity in GOG-232B (response rate of 54%). Subsequently, GOG-261 established PAC/CARBO as the new standard initial therapy for this rare disease.⁴⁴

Uterine Sarcomas

Evaluation of Gemcitabine and Docetaxel in Uterine Leiomyosarcoma (87 and 131 series)

The GOG ran two phase II trials of gemcitabine and docetaxel, one in first line (87-L) and one in second-line therapy (131-G)⁴⁵ confirming the activity of this regimen. A randomized phase II trial was then led by the Sarcoma Alliance for Research through Collaboration (SARC 002), to allow for inclusion of all patients with metastatic soft tissue sarcomas (not just uterine LMS), that confirmed the superiority of docetaxel/gemcitabine to single agent gemcitabine both in terms of PFS and OS and effected a

change in standard practice for this disease. The GOG completed a phase III trial of gemcitabine and docetaxel with and without bevacizumab (GOG-250)⁴⁶ which showed no benefit for the addition of bevacizumab to gemcitabine and docetaxel. Although SARC005⁴⁷ showed promising results, GOG-277,⁴⁸ a phase III randomized trial of gemcitabine plus docetaxel followed by doxorubicin versus observation for uterus-limited, high grade uterine LMS was closed early for slow enrollment, but in the limited (underpowered) dataset (n=38 of a planned 216), it appeared there was no benefit of adjuvant chemotherapy over observation alone in this population.

Epithelial Ovarian Cancer

Front-line therapy studies

The usual initial therapy of epithelial ovarian cancer (EOC) involves treatment with a taxane and a platinum agent. This therapy is either delivered in the form of paclitaxel and carboplatin, dose dense (weekly) paclitaxel and carboplatin or intraperitoneal (IP) therapy. Despite an NCI clinical announcement in 2006 (following the publication of GOG-172)⁴⁹ declaring IP the preferred method of treatment for stage III, optimally debulked EOC; use of this treatment remained low. DTC prioritized the development of intraperitoneal (IP) regimens with the goal of reduced toxicity, while maintaining or increasing efficacy. The Phase I Subcommittee completed three phase I studies incorporating dose/schedule modifications, IP carboplatin (instead of IP cisplatin), docetaxel (instead of paclitaxel), and an assessment of the safety and feasibility of adding IV bevacizumab on Day 1. GOG-9916⁵⁰ evaluated three regimens, Part A (Day 1: IV paclitaxel and IP carboplatin, Day 8: IP paclitaxel), Part B (Day 1: IV docetaxel and IP carboplatin, Day 8: IP paclitaxel), and Part C (bevacizumab successfully added to Part A regimen). Part B cycle 1 MTD was not feasible over four cycles due to bone marrow toxicity. GOG-9917⁵¹ established chemotherapy doses (Day 1: IV paclitaxel 175 mg/m² and IP carboplatin AUC 5 +/- bevacizumab) of every three-week regimen. Of note, GOG-9917 includes a successful collaboration with the Kawasaki Medical School in Kurashiki-City, Japan, a member of the Japanese GOG consortium. GOG-9921⁵² successfully identified a modified GOG-172 regimen of IV/IP paclitaxel and IP cisplatin (Day 1: IV paclitaxel 135 mg/m² over 3 hours and IP cisplatin 75 mg/m², Day 8: IP paclitaxel 60mg/m²) that allowed for 95% of patients to complete all 6 cycles of therapy. In comparison, only 42% of patients on the IP arm of GOG-172 completed the planned 6 cycles of therapy. GOG-9916 and 9917 contributed to the IP carboplatin arm used for phase III testing by the Ovarian Committee (GOG252) and GOG9921 (modified 172 regimen) was the standard therapy and control arm (GOG252).

Next, DT investigated two front-line strategies incorporating targeted therapies into the carboplatin/paclitaxel backbone (GOG-9923 and the safety lead-in of GY007). GOG-9923,⁵³ a phase I study of chemotherapy and bevacizumab with the PARP inhibitor, veliparib, in patients with previously untreated EOC, determined the maximum tolerated dose and dose-limiting toxicities of intermittent and continuous dosing of veliparib (ABT-888) when administered with either IV carboplatin/paclitaxel/bevacizumab or IP cisplatin/IV and IP paclitaxel/bevacizumab. This large phase I study enrolled 424 patients across six dosing schedules. This study showed it was feasible to combine a PARP inhibitor with chemotherapy without compromising dose intensity. In parallel DTC performed GOG-280,⁵⁴ a phase II trial of veliparib in the proof of principle (BRCA germ line mutation) recurrent population, establishing activity. GOG-9923 ultimately informed the dose that moved forward in the phase III trial GOG-3005/Velia (NCT02470585). This study was awarded a CTEP Career Development LOI (CRDL) and an American Reinvestment and Recovery Act Award (ARRA).

The Phase I Subcommittee led the phase I portion of GY00755, a phase I/II study of the JAK/STAT inhibitor ruxolitinib with front-line neoadjuvant and post-surgical chemotherapy. The study identified a feasible dose of ruxolitinib when combined with carboplatin AUC 5 and paclitaxel 70mg/m² and enrollment to the randomized phase II portion of the study was completed in October 2019. With a median follow-up of 24 months, the median PFS was 14.6 months with ruxolitinib plus chemotherapy vs 11.6 months for chemotherapy alone (HR, 0.70; 90% CI, 0.00-0.89; log rank P = .059). Analysis of overall survival showed a hazard ratio of 0.785 favoring the experimental arm (1-sided 90% CI, 0.44-1.39; log-rank P = .70).⁵⁵

IP Studies

The Phase I Subcommittee completed two studies evaluating targeted agents delivered IP for patients with persistent or recurrent disease. In GOG-9924,⁵⁷ a phase I pharmacokinetic study of intraperitoneal bortezomib (proteasome inhibitor) and carboplatin, a feasible dose of bortezomib was identified but required decreasing the dose intensity of carboplatin. In GOG-9928, a phase I study of intraperitoneal EGEN-001 (interleukin-12 plasmid formulated with peg-pep-cholesterol lipopolymer) administered in combination with pegylated liposomal doxorubicin, there were no DLTs and a maximum tolerated dose was identified. Neither combination was brought forward for study in phase II.

Studies for Platinum-Sensitive Disease

The Phase I Subcommittee completed a study evaluating

the addition of veliparib to liposomal doxorubicin and carboplatin with bevacizumab for patients with platinum-sensitive recurrent disease (GOG-9927).⁵⁸ The combination resulted in significant toxicities limiting the utility of this approach. Safety lead-ins were also conducted by the DTC/Phase I Subcommittee for GY004, a phase III study comparing single-agent olaparib or the combination of cediranib and olaparib to standard platinum-based chemotherapy, and GY021, a phase II randomized trial of olaparib plus tremelimumab versus olaparib alone.

Platinum Resistant Studies

Single-arm phase II trials in platinum resistant ovarian cancer (126 series). The GOG has demonstrated the activity of re-treatment with taxanes in platinum-taxane resistant EOC. In the GOG 126 series, patients with one prior therapy (initial taxane plus platinum-therapy) who progress within 6 months of their last platinum dose are entered. Docetaxel (126J),⁵⁹ weekly paclitaxel (126N)⁶⁰ and weekly albumin bound paclitaxel (126R)⁶¹ have all shown activity, with ORR of 21-23%. This consistent and reproducible activity of taxane retreatment has contributed to weekly paclitaxel being a common usual care option for patients and serving as a chemotherapy backbone for development of novel combinations in randomized phase II and III trials. Pemetrexed also showed activity in the 126 series with a 21% response rate (126Q).⁶²

Among other interesting agents, antibody drug conjugates are emerging as very active drugs in the PROC setting. Currently, the GOG-F has GOG 3048/UPLIFT accruing as a single arm phase II of the ADC Upifitamab Rilsodotin (NCT03319628) with a randomized phase III trial of this agent currently accruing for the platinum sensitive recurrent setting (UPNEXT: NCT05329545).

Randomized Phase II Trials in Platinum Resistant Ovarian Cancer (186 series)

In 2002, the 186 series was initiated for patients with one to three prior lines of chemotherapy. The initial studies in this series were single-arm studies that required measurable disease and had a traditional response rate endpoint. In 2010, the 186 series evolved from serial evaluation of single agents to randomized phase II trials. These randomized phase II trials allowed for more effective evaluation of efficacy (as compared to relying on historical controls), the ability to evaluate novel combinations, and the ability to evaluate different doses and schedule. The endpoint for these studies was progression free survival. Five randomized studies incorporating either a weekly paclitaxel backbone or bevacizumab backbone were completed. These included weekly paclitaxel with and without Reolysin (186H),⁶³

weekly paclitaxel with pazopanib versus placebo (186J),⁶⁴ weekly paclitaxel versus cabozantinib (186K),⁶⁵ bevacizumab with everolimus versus placebo (186G)⁶⁶ and bevacizumab with and without fosbretabulin (186I).⁶⁷ None of these studies showed a survival benefit for the experimental arm. The 186 series was discontinued in the restructuring of GOG to NRG. A phase II trial of elesclomol, a pro-apoptotic agent, and weekly paclitaxel for platinum-resistant recurrent disease (GOG260)⁶⁸ similarly showed no significant survival benefit for the combination.

The randomized phase II program allowed evaluation of novel combinations and to draw in the accrual power of the entire GOG membership as many sites declined participation in smaller phase II studies due to the complexity of opening the studies with limited accrual.

Immunotherapy Studies

The incorporation of immunotherapy for the treatment of recurrent EOC has been an area of great interest. In collaboration with CTEP and the pharmaceutical industry, the GOG completed a phase I trial (GOG-9925)⁶⁹ of VTX-2337 in combination with pegylated liposomal doxorubicin (PLD) or weekly paclitaxel. One of the most basic mechanisms for activation of the immune system is through Toll-like receptors (TLRs). The combination of a specific TLR agonist with the capacity to activate dendritic cells and monocytes can be shown in pre-clinical models to provide synergy with chemotherapy and stimulate a variety of immune pathways relevant to generation of anti-tumor immunity. VTX-2337 is a novel small molecule TLR8 agonist. After establishing safety and recommended phase II dose in 9925, GOG-3003, a randomized phase II trial of PLD with VTX-2337 versus placebo, was launched.

Incorporation of Targeted Therapy and Immunomodulatory Agents in Ovary Cancer (170 series)

The 170 series is a series of phase II trials of targeted and immunomodulatory agents in patients with recurrent EOC who have received 1-2 prior lines of therapy. Overall, this series of studies has been disappointing in terms of demonstrating activity. The only truly positive phase II trial performed in this series is GOG-170D;⁷⁰ a phase II trial of bevacizumab. This trial resulted in an impressive ORR of 21% with 40% of patients surviving and progression free at 6 months. With this activity, a front-line Phase III trial (GOG-218)⁷¹ which evaluated chemotherapy with or without bevacizumab, as well as maintenance bevacizumab, was performed. This phase III trial documented a significant improvement in progression-free survival with the addition of bevacizumab.

DTC completed a phase II study of nivolumab versus

nivolumab and ipilimumab (GY00372). The combination showed an improved response rate (12% vs 31%) and a slightly longer median progression free survival (two months versus 3.9 months). The Phase I Subcommittee conducted the safety lead-in for GY009, a randomized, phase II/III study of pegylated liposomal doxorubicin and atezolizumab versus pegylated liposomal doxorubicin/bevacizumab in platinum resistant ovarian cancer. The phase III portion of the study completed accrual in October 2021 and results are maturing.

Targeted Therapies for Clear Cell Ovarian Carcinomas

DTC has conducted two studies evaluating targeted therapies for clear cell ovarian cancers. GY001,⁷³ a phase II trial of cabozantinib (a TKI primarily targeting c-MET) for recurrent disease, unfortunately, demonstrated minimal activity. GY014, a phase II study of tazemetostat (an oral EZH2 inhibitor) in recurrent or persistent endometrioid or clear cell carcinoma of the ovary, and recurrent or persistent endometrioid endometrial adenocarcinoma, completed first stage accrual with promising results in ARID1A mutated, clear cell ovarian cancer and completed accrual.

Disease Agnostic

In 2019 the Developmental Therapeutics Committee extended its portfolio to include early-phase disease agnostic studies. GY022 represents the first such study. This pharmacokinetic study will assess predictors of carboplatin clearance using the contrast agent iohexol in patients undergoing carboplatin treatment on a clinical trial or as standard of care treatment.

The NCI-ComboMATCH Precision Medicine Cancer trial (EAY191)⁵⁶ is an ECOG-ACRIN led successor to the NCI-MATCH study. The NCI-ComboMATCH will explore genomically-directed novel combinations of targeted drugs supported by robust in vivo evidence including patient-derived (PDx) and cell-line-derived (CDx) data. Each of the five lead protocol organizations in the NCI Clinical Trials Network (NCTN) will manage a cassette of subprotocols. DT, led by Dr O'Cearbhaill, will oversee the NRG Oncology subprotocols (EAY191-Nx) which will include genomically selected disease-site agnostic as well as disease-site specific cohorts. The phase I committee will help obtain safety data for combinations with strong preclinical data but lacking safety data so that they can be considered for future arms once that data is obtained.

Future Plans

The Developmental Therapeutics Committee will continue to provide NRG Oncology with a diverse portfolio of cytotoxic, targeted, and immunomodulatory agents for Phase I and single arm Phase II studies for women with

gynecologic cancers in collaboration with NCI's CTEP and the pharmaceutical industry. These studies will evaluate new investigational agents and combinations of agents, novel scheduling and dosing of investigational and non-investigational agents, and novel concurrent chemotherapy and radiation therapy regimens, based on preclinical or early clinical data. The DTC will actively facilitate collaboration with Disease Site Committees, to ensure that appropriate agents are prioritized for development with an aim toward future randomized phase II and phase III trials. Integral biomarkers and translational research in these trials will continue to evolve and strengthen as scientific information becomes available.

The DTC has recently expanded its repertoire to include early-phase, disease-site agnostic studies. The Phase I Subcommittee encourages individual member sites to expand multi-disciplinary participation in anticipation of the development of basket studies. Future studies are likely to involve the investigation of multiple diverse agents including chemotherapy, targeted agents, immunotherapy, radio-sensitizers, combination regimens, possibly in combination with radiotherapy. In 2021, seven additional phase I sites were selected to join the Subcommittee for a total of 30 active sites.

In 2020, the Pharmaceutical Research and Manufacturers of America website reported that there were more than 1,300 agents in clinical development for cancer. In addition, there has been an explosion of genomic data across many solid tumors demonstrating that these tumors are molecularly complex often containing more than one driver mutation. Taken together, it is critical to consider innovative trial designs. In concert with the members of the Committee on Experimental Medicine and the NRG Oncology biostatisticians, these designs often require acquisition of tumor tissue, blood and plasma. Moreover, these designs will necessitate: 1) Randomized trial designs that allow for early introduction of combinations, a necessary shift from serial evaluation of single targeted agents; 2) adaptive trial designs that allow for randomization of multiple treatment options based on pre-defined molecular biomarkers of the tumor with treatment changes based on emerging results from the trial; and 3) novel trial designs that allow for diseases with similar histologic and/or molecular characteristics (i.e., serous ovarian cancer and serous endometrial cancer or HPV-positive squamous cell carcinomas of the cervix, vagina, and vulva) to receive the same treatment in a single-trial.

The NCI-ComboMATCH Precision Medicine Cancer trial (EAY191)⁵⁶ is an ECOG-ACRIN led successor to the NCI-

MATCH study. Each of the five lead protocol organizations in the NCI Clinical Trials Network (NCTN) manages a cassette of subprotocols. The EAY191-Nx subprotocols will be led by NRG Oncology and will explore genomically-directed novel combinations of targeted drugs supported by robust in vivo evidence including patient-derived (PDx) and cell-line-derived (CDx) data.

These complex phase I/II studies and collaboration with other lead protocol organizations require specialized staff. The overall process has benefited from designation of key individuals in both GOG's Administrative Office and the Statistical and Data Center devoted to protocol development, translational objectives, and statistical endpoints. The unique web-based NRG Oncology Phase I infrastructure, which effectively monitors patients and manages the NRG Oncology Phase I trials in real-time, ensures the safety of all patients on Phase I trials and Phase II/III safety lead-ins and allows for the appropriate dose escalation. Furthermore, bi-weekly Phase I and Phase II safety-lead in conference calls involving Study Chair, Phase I Subcommittee Chair, DT Chair, SDC biostatistician, SDC Clinical Data Coordinator, and representation from all sites with patients accrued (investigator and/or research nurse); allows for in depth review of all data including safety information (AdEERS Reports) in real time. Thus, the current DTC is well-positioned to assist NRG Oncology in the development of innovative Phase I and II regimens for future randomized phase II and phase III studies in people with gynecologic cancers.

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References

1. GOG-9803, DiSilvestro P, Walker J, Morrison A, Rose PG, Homesley H, Warshal D. Radiation therapy with concomitant paclitaxel and cisplatin chemotherapy in patients with cervical carcinoma limited to the pelvis: a phase I/II study of the Gynecologic Oncology Group. *Gynecol Oncol.* 103: 1038-1042, 2006.
2. GOG-9804, Walker JL, Morrison A, DiSilvestro P, Von Gruenigen, V. A phase I/II study of extended field radiation therapy with concomitant paclitaxel and cisplatin chemotherapy in patients with cervical carcinoma metastatic to the para-aortic lymph nodes: a Gynecologic Oncology Group study. *Gynecol Oncol.* 112(1): 78-84, 2009.
3. GOG-9912, Rose PG, DeGeest K, McMeekin DS, Fusco

- N. A phase I study of gemcitabine followed by cisplatin concurrent with whole pelvic radiation therapy in locally advanced cervical cancer: A Gynecologic Oncology Group Study. *Gynecol Oncol*. 107: 274-9, 2007.
- GOG-9913, Rose PG, Sill MW, McMeekin DS, Ahmed A, Salani R, Yamada SD, Wolfson A, Fusco N, Fracasso PM. A phase I study of concurrent weekly topotecan and cisplatin chemotherapy with whole pelvic radiation therapy in locally advanced cervical cancer: A Gynecologic Oncology Group study. *Gynecol Oncol*. 125: 158-62, 2012.
 - GOG-9918, Moore KN, Sill M, Miller DS, McCourt CK, De Geest K, Rose PG, Cardenes HR, Mannel RS, Farley JH, Schilder RJ, Fracasso PM. A phase I trial of tailored radiation therapy with concomitant cetuximab and cisplatin in the treatment of patients with cervical cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 127(3): 456-61, 2012
 - GOG-9926. Boardman CH., Brady WE, Dizon DS, Kunos CA, Moore KN, Zanotti KM, Matthews C, Cosin JA, Aghajanian C, Fracasso PM. A phase I evaluation of extended field radiation therapy with concomitant cisplatin chemotherapy followed by paclitaxel and carboplatin chemotherapy in women with cervical carcinoma metastatic to the para-aortic lymph nodes: An NRG Oncology/Gynecologic Oncology Group Study. *Gynecol Oncol*. Nov15(2)202-207.2018.
 - NRG GY0274 . Mileschkin, LR; Moore, KN; Barnes,E; GebSKI, V; Narayan, K; Bradshaw, N; Lee,YC; Diamante, K; Fyles, AW; Small, W; Gaffney, DK; Khaw, P; Brooks, S; Thompson, JS; Huh,WK; Carlson, M; Mathews, CA; Rischin, D; Stockler, MR; and Monk, BJ. Adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: The randomized phase III OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274). *Journal of Clinical Oncology*.2021 39:18_suppl, LBA3-LBA3
 - GOG-76S, McGuire WP, Blessing JA, Moore D, Lentz SS, Photopoulos G. Paclitaxel has Moderate Activity in Squamous Cervix Cancer: A Gynecologic Oncology Group Study. *J Clin Oncol* 14(3): 792-795, 1996.
 - GOG-76X, Rose PG, Blessing JA, Gershenson DM, McGehee R. Paclitaxel and Cisplatin as First-line Therapy in Recurrent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study. *J Clin Oncol* 17: 2676- 2680, 1999.
 - GOG-169, Moore DH, Blessing JA, McQuellon, Thaler HT, Cella D, Benda J, Miller DS, Olt G, King S, Boggess JF, Rocereto TF. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent or persistent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. *J Clin Oncol* 22(15): 3113-9, 2004.
 - GOG-76U, Muderspach LI, Blessing JA, Levenback C, Moore JR. A phase II trial of topotecan in patients with squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. *Gynecol Oncol* 81(2): 213-215, 2001.
 - GOG-127F, Bookman MA, Blessing JA, Hanjani P, Herzog TJ, Andersen WA. Topotecan in squamous cell carcinoma of the cervix: A phase II Gynecologic Oncology Group study. *Gynecol Oncol*. 77(3): 446-449, 2000.
 - GOG-179, Long HJ, Bundy BN, Grendys EC, Benda J, McMeekin DS, Sorosky J, Miller DS, Eaton LA, Fiorica JV. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *J Clin Oncol* 23(21): 4626-33, 2005.
 - GOG-76Z, Morris M, Blessing JA, Monk B, McGehee R, Moore D. Phase II study of cisplatin and vinorelbine in squamous cell carcinoma of the cervix: a GOG study. *J Clin Oncol* 22(16): 3340-4, 2004.
 - GOG-127Q, Brewer CA, Blessing JA, Nagourney RA, McMeekin DS, Lele S, Zweizig SL. Cisplatin plus gemcitabine in previously treated squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol*. 100: 385-88, 2006.
 - GOG-204, Monk BJ, Sill MW, McMeekin DS, Cohn D, Ramondetta L, Boardman CH, Benda J. Randomized phase III trial of four cisplatin containing doublet combinations in stage IVB, recurrent or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol* 27(28): 4649-55, 2009.
 - GOG-76GG, Miller DS, Blessing JA, Ramondetta LM, Pham HQ, Tewari KS, Landrum LM, Brown J, Mannel RS. Pemetrexed and cisplatin for the treatment of advanced, persistent, or recurrent carcinoma of the cervix: a limited access phase II trial of the gynecologic

- logic oncology group. *J Clin Oncol*. 2014 Sep 1;32(25):2744-9
18. GOG-76HH, Thaker PH, Salani R, Brady WE, Lankes HA, Cohn DE, Mutch DG, Mannel RS, Bell-McGuinn KM, Di Silvestro PA, Jelovac D, Carter JS, Duan W, Resnick KE, Dizon DS, Aghajanian C, Fracasso PM. A phase I trial of paclitaxel, cisplatin, and veliparib in the treatment of persistent or recurrent carcinoma of the cervix: an NRG Oncology Study (NCT#01281852). *Ann Oncol*. 2017 Mar 1;28(3):505-511.
 19. GOG-3023, Coleman RL, Lorusso D, Gennigens C, González-Martín A, Randall L, Cibula D, Lund B, Woelber L, Pignata S, Forget F, Redondo A, Vindeløv SD, Chen M, Harris JR, Smith M, Nicacio LV, Teng MSL, Laenen A, Rangwala R, Manso L, Mirza M, Monk BJ, Vergote I; innovaTV 204/GOG-3023/ENGOT-cx6 Collaborators. Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol*. 2021 May;22(5):609-619. doi: 10.1016/S1470-2045(21)00056-5. Epub 2021 Apr 9. PMID: 33845034.
 20. GOG-227C, Monk BJ, Sill MW, Burger RA, Gray HJ, Buekers TE, Roman LD. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. *J Clin Oncol* 27(7): 1069-74, 2009.
 21. GOG-240, Chase D, Huang HQ, Monk BJ, Ramondetta LM, Penson RT, Gil K, Landrum LM, Leitao M, Oaknin A, Huh WK, Pulaski HL, Robison K, Guntupalli SR, Richardson D, Salani R, Sill MW, Wenzel LB, Tewari KS. Patient-reported outcomes at discontinuation of anti-angiogenesis therapy in the randomized trial of chemotherapy with bevacizumab for advanced cervical cancer: an NRG Oncology Group study. *Int J Gynecol Cancer*. 2020 May;30(5):596-601
 22. Tewari KS, Sill MW, Penson RT, et al: Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet* 390:1654-1663, 2017
 23. GOG-9929, Mayadev JS, Enserro D, Lin YG, Da Silva DM, Lankes HA, Aghajanian C, Ghamande S, Moore KN, Kennedy VA, Fracasso PM, Schilder RJ. Sequential Ipilimumab After Chemoradiotherapy in Curative-Intent Treatment of Patients With Node-Positive Cervical Cancer. *JAMA Oncol*. 2020 Jan 1; 6(1):92-99.
 24. NRG GY002, Santin AD, Deng W, Frumovitz M, Buza N, Bellone S, Huh W, Khleif S, Lankes HA, Ratner ES, O'Ceirbhail RE, Jazaeri AA, Birrer M. Phase II evaluation of nivolumab in the treatment of persistent or recurrent cervical cancer (NCT02257528/NRG-GY002). *Gynecol Oncol*. 2020 Apr;157(1):161-166.
 25. GOG-265 Huh WK, Brady WE, Fracasso PM, Dizon DS, Powell MA, Monk BJ, Leath CA 3rd, Landrum LM, Tanner EJ, Crane EK, Ueda S, McHale MT, Aghajanian C. Phase II study of axalimogene filolisbac (ADXS-HPV) for platinum-refractory cervical carcinoma: An NRG oncology/gynecologic oncology group study. *Gynecol Oncol*. 2020 Sep;158(3):562-569.
 26. GOG 3016, Tewari KS, Monk BJ, Vergote I, Miller A, de Melo AC, Kim HS, Kim YM, Lisyanskaya A, Samouëlian V, Lorusso D, Damian F, Chang CL, Gotovkin EA, Takahashi S, Ramone D, Pikiel J, Maćkowiak-Matejczyk B, Guerra Alía EM, Colombo N, Makarova Y, Rischin D, Lheureux S, Hasegawa K, Fujiwara K, Li J, Jamil S, Jankovic V, Chen CI, Seebach F, Weinreich DM, Yancopoulos GD, Lowy I, Mathias M, Fury MG, Oaknin A; Investigators for GOG Protocol 3016 and ENGOT Protocol En-Cx9. Survival with Cemiplimab in Recurrent Cervical Cancer. *N Engl J Med*. 2022 Feb 10;386(6):544-555. doi: 10.1056/NEJMoa2112187. PMID: 35139273.
 27. KEYNOTE 826, Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, Tewari KS, Salman P, Hoyos Usta E, Yañez E, Gümüş M, Olivera Hurtado de Mendoza M, Samouëlian V, Castonguay V, Arkhipov A, Toker S, Li K, Keefe SM, Monk BJ; KEYNOTE-826 Investigators. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. *N Engl J Med*. 2021 Nov 11;385(20):1856-1867. doi: 10.1056/NEJMoa2112435. Epub 2021 Sep 18. PMID: 34534429.
 28. GOG-86O, Ball H, Blessing JA, Lentz SS, Mutch D. A Phase II Trial of Paclitaxel in Patients with Advanced or Recurrent Adenocarcinoma of the Endometrium: A Gynecologic Oncology Group Study. *Gynecol Oncol* 62: 278-281, 1996.
 29. GOG-129C, Lincoln S, Blessing JA, Lee RB, Rocereto TF. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 88(3): 277-81, 2003.
 30. GOG-177, Fleming GF, Brunetto VL, Cella D, Look KY, Reid G, Munkarah A, Kline R, Burger RA, Goodman A, Burks RT. Phase III trial of doxorubicin plus cisplatin

with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* 22(11): 2159-66, 2004.

31. GOG-209, Miller DS, Filiaci VL, Mannel RS, Cohn DE, Matsumoto T, Tewari KS, DiSilvestro P, Pearl ML, Argenta PA, Powell MA, Zweizig SL, Warshal DP, Hanjani P, Carney ME, Huang H, Cella D, Zaino R, Fleming GF. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). *J Clin Oncol*. 2020 Nov 20;38(33):3841-3850.
32. GOG-229E, Aghajanian C, Sill MW, Darcy KM, Greer B, McMeekin DS, Rose PG, Rotmensch J, Barnes MN, Hanjani P, Leslie KK. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 29(16): 2259-65, 2011.
33. GOG-86P, Aghajanian C, Filiaci VL, Dizon DS, et al: A randomized phase II study of paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus and ixabepilone/carboplatin/bevacizumab as initial therapy for measurable stage III or IVA, stage IVB or recurrent endometrial cancer. *Journal of Clinical Oncology* 33, 2015
34. GOG-86P, Aghajanian C, Filiaci V, Dizon DS, et al: A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. *Gynecologic Oncology* 150:274-281, 2018
35. GOG-248, Fleming GF, Filiaci VL, Marzullo B, Zaino RJ, Davidson SA, Pearl M, Makker V, Burke JJ 2nd, Zweizig SL, Van Le L, Hanjani P, Downey G, Walker JL, Reyes HD, Leslie KK. Temsirolimus with or without megestrol acetate and tamoxifen for endometrial cancer: a gynecologic oncology group study. *Gynecol Oncol*. 2014 Mar;132(3):585-92.
36. GOG-229O, Westin SN, Sill MW, Coleman RL, Waggoner S, Moore KN, Mathews CA, Martin LP, Modesitt SC, Lee S, Ju Z, Mills GB, Schilder RJ, Fracasso PM, Birrer MJ, Aghajanian C. Safety lead-in of the MEK inhibitor trametinib in combination with GSK2141795, an AKT inhibitor, in patients with recurrent endometrial cancer: An NRG Oncology/GOG study. *Gynecol Oncol*. 2019 Dec;155(3):420-428.
37. GOG229J, Bender D, Sill MW, Lankes HA, Reyes HD, Darus CJ, Delmore JE, Rotmensch J, Gray HJ, Mannel RS, Schilder JM, et al. A phase II evaluation of cediranib in the treatment of recurrent or persistent endometrial cancer: An NRG Oncology/ Gynecologic Oncology Group study. *Gynecol Oncol*. 2015 Sep;138(3):507-12.
38. NRG GY012, Mackay H, Rimel B, Bender D, A randomized phase II study comparing single-agent olaparib, single agent cediranib, and the combination of cediranib/olaparib in women with recurrent, persistent or metastatic endometrial cancer. *Journal of Clinical Oncology* 37, 2019
39. NRG GY008, Santin AD, Filiaci V, Bellone S, O'Ceirbhail R, Ratner ES, Mathews CA, Cantuaria G, Gundersen CC, Rutledge T, Buttin BM, Lankes HA, Birrer MJ. Corrigendum to "Phase II evaluation of copanlisib, a selective inhibitor of Pi3kca, in patients with persistent or recurrent endometrial carcinoma harboring PIK3CA hotspot mutations: An NRG oncology study (NRG-GY008)" [*Gynecol. Oncol. Rep.* 31 (2020) 100532]. *Gynecol Oncol Rep*. 2020 May 28; 33:100590.
40. NRG GY008, Santin AD, Filiaci V, Bellone S, et al: Phase II evaluation of copanlisib, a selective inhibitor of Pi3kca, in patients with persistent or recurrent endometrial carcinoma harboring PIK3CA hotspot mutations: An NRG Oncology study (NRG-GY008). *Gynecologic Oncology Reports* 31, 2020
41. GOG 3007, Slomovitz BM, Filiaci VL, Walker JL, Taub MC, Finkelstein KA, Moroney JW, Fleury AC, Muller CY, Holman LL, Copeland LJ, Miller DS, Coleman RL. A randomized phase II trial of everolimus and letrozole or hormonal therapy in women with advanced, persistent or recurrent endometrial carcinoma: A GOG Foundation study. *Gynecol Oncol*. 2022 Jan 18:S0090-8258(21)01699-1. doi: 10.1016/j.ygyno.2021.12.031. Epub ahead of print. PMID: 35063278.
42. NRG GY011, Duska LR, Filiaci VL, Walker JL, Holman LL, Hill EK, Moore RG, Ring KL, Pearl ML, Muller CY, Kushnir CL, Lankes HA, Samuelson MI, Carrick KS, Rajan A, Rodgers WH, Kohn EC, Piekarcz R, Leslie KK. A Surgical Window Trial Evaluating Medroxyprogesterone Acetate with or without Entinostat in Patients with Endometrial Cancer and Validation of Biomarkers of Cellular Response. *Clin Cancer Res*. 2021 May 15;27(10):2734-2741.
43. GOG-130B, Curtin JP, Blessing JA, Soper JT, DeGeest K. Paclitaxel in the treatment of carcinosarcoma of

- the uterus: A Gynecologic Oncology Group study. *Gynecol Oncol.* 83(2): 268-270, 2001.
44. GOG-261, Powell MA, Filiaci VL, Hensley ML, Huang HQ, Moore KN, Tewari KS, Copeland LJ, Secord AA, Mutch DG, Santin A, Warshal DP, Spiratos NM, DiSilvestro PA, Ioffe OB, Miller DS. Randomized Phase III Trial of Paclitaxel and Carboplatin Versus Paclitaxel and Ifosfamide in Patients With Carcinosarcoma of the Uterus or Ovary: An NRG Oncology Trial. *J Clin Oncol.* 2022 Jan 10: JCO2102050. doi: 10.1200/JCO.21.02050. Epub ahead of print. PMID: 35007153.
 45. GOG-131G, Hensley M, Blessing J, DeGeest K, Abulafia O, Rose P, Homesley H. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: A Gynecologic Oncology Group phase II study. *Gynecol Oncol.* 109(3): 323-8, 2008.
 46. GOG-250, Hensley ML, Miller A, O'Malley DM, Mannel RS, Behbakht K, Bakkum-Gamez JN, Michael H. Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/Gynecologic Oncology Group study. *J Clin Oncol.* 2015 Apr 1;33(10):1180-5.
 47. SARC005, Hensley ML, Wathen K, Maki RG, et al: Adjuvant treatment of high-risk primary uterine leiomyosarcoma with gemcitabine/docetaxel (GT), followed by doxorubicin (D): Results of phase II multicenter trial SARC005. *Journal of Clinical Oncology* 28, 2010
 48. GOG-277, Hensley ML, Enserro D, Hatcher H, Ottavanger PB, Krarup-Hansen A, Blay JY, Fisher C, Moxley KM, Lele SB, Lea JS, Tewari KS, Thaker PH, Zivanovic O, O'Malley DM, Robison K, Miller DS. Adjuvant Gemcitabine Plus Docetaxel Followed by Doxorubicin Versus Observation for High-Grade Uterine Leiomyosarcoma: A Phase III NRG Oncology/Gynecologic Oncology Group Study. *J Clin Oncol.* 2018 Oct 5: JCO1800454.
 49. GOG-172, Armstrong DK, Bundy BN, Wenzel L, Huang HQ, Baergen R, Lele SB, Copeland LJ, Walker JL, Burger RA. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 354(1): 34-43, 2006.
 50. GOG-9916, Gould N, Sill MW, Mannel RS, Thaker PK, DiSilvestro P, Waggoner S, Yamada SD, Armstrong DK, Fracasso P, Wenzel L, Huang H, Walker JL. A phase I study with an expanded cohort to assess the feasibility of intravenous paclitaxel, intraperitoneal carboplatin, and intraperitoneal paclitaxel in patients with untreated ovarian, fallopian tube or primary peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 125: 54-58, 2012.
 51. GOG-9917, Morgan MA, Sill MW, Fujiwara K, Greer B, Rubin S, DeGeest K, Yamada SD, Waggoner S, Coleman RL, Walker JL, Mannel RS. A phase I study with an expanded cohort to assess the feasibility of intraperitoneal carboplatin and intravenous paclitaxel in untreated ovarian, fallopian tube, and primary peritoneal carcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol.* 121(2): 264-8, 2011.
 52. GOG-9921, Dizon DS, Sill MW, Gould N, Rubin SC, Yamada SD, Debernardo RL, Mannel RS, Eisenhauer EL, Duska LR, Fracasso PM. Phase I feasibility study of intraperitoneal cisplatin and intravenous paclitaxel followed by intraperitoneal paclitaxel in untreated ovarian, fallopian tube, and primary peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 123(2): 182-6, 2011.
 53. GOG-9923 Moore, K. N., Miller, A., Bell-McGuinn, K. M., Schilder, R. J., Walker, J. L., O'Cearbhaill, R. E., Guntupalli, S. R., Armstrong, D. K., Hagemann, A. R., Gray, H. J., Duska, L. R., Mathews, C. A., Chen, A., O'Malley, D., Gordon, S., Fracasso, P. M., & Aghajanian, C. (2020). A phase I study of intravenous or intraperitoneal platinum-based chemotherapy in combination with veliparib and bevacizumab in newly diagnosed ovarian, primary peritoneal and fallopian tube cancer. *Gynecol Oncol.* 156(1), 13–22.
 54. GOG-280, Coleman RL, Sill MW, Bell-McGuinn K, et al: A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation - An NRG Oncology/Gynecologic Oncology Group study. *Gynecologic Oncology* 137:386-391, 2015
 55. NRG GY007, Landen CN, Buckanovich RJ, Sill M, et al: A phase I/II study of ruxolitinib with frontline neoadjuvant and post-surgical therapy in patients with advanced epithelial ovarian, Fallopian tube, or primary peritoneal cancer. *Journal of Clinical Oncology* 40, 2022

56. EAY191, Meric-Bernstam, F; James M. Ford, Peter J. O'Dwyer, Geoffrey I. Shapiro, Lisa M. McShane, Boris Freidlin, Roisin E. O'Cearbhaill, Suzanne George, Julia Glade-Bender, Gary H. Lyman, James V. Tricoli, David Patton, Stanley R. Hamilton, Robert J. Gray, Douglas S. Hawkins, Bhanumati Ramineni, Keith T. Flaherty, Petros Grivas, Timothy A. Yap, Jordan Berlin, James H. Doroshow, Lyndsay N. Harris, Jeffrey A. Moscow; on behalf of ComboMATCH study team, National Cancer Institute Combination Therapy Platform Trial with Molecular Analysis for Therapy Choice (ComboMATCH). *Clin Cancer Res* 15 April 2023; 29 (8): 1412-1422. <https://doi.org/10.1158/1078-0432.CCR-22-3334>
57. GOG-9924, A phase I pharmacokinetic study of intraperitoneal bortezomib and carboplatin in patients with persistent or recurrent ovarian cancer: An NRG Oncology/Gynecologic Oncology Group study. Jandial DA, Brady WE, Howell SB, Lankes HA, Schilder RJ, Beumer JH, Christner SM, Strychor S, Powell MA, Hagemann AR, Moore KN, Walker JL, DiSilvestro PA, Duska LR, Fracasso PM, Dizon DS. *Gynecol Oncol.* 145(2):236-242, 2017.
58. GOG-9927, Landrum LM, Brady WE, Armstrong DK, Moore KN, DiSilvestro PA, O'Malley DM, Tenney ME, Rose PG, Fracasso PM. A phase I trial of pegylated liposomal doxorubicin (PLD), carboplatin, bevacizumab and veliparib in recurrent, platinum-sensitive ovarian, primary peritoneal, and fallopian tube cancer: An NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol.* 140(2):204-9, 2016.
59. GOG-126J, Rose P, Blessing J, Ball H, Hoffman J, Warshal D, DeGeest K, Moore D. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol* 88(2): 130-5, 2003.
60. GOG-126N, Markman M, Blessing J, Rubin S, Connor J, Hanjani P, Waggoner S. Phase II trial of weekly paclitaxel (80 mg/m²) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. *Gynecol Oncol.* 101: 436-440, 2006.
61. GOG-126-R, Coleman RL, Brady WE, McMeekin DS, Rose PG, Soper JT, Lentz SS, Hoffman JS, Shahin MS. A phase II evaluation of nanoparticle, albumin-bound (nab) paclitaxel in the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: a Gynecologic Oncology Group study. *Gynecol Oncol.* 122(1): 111- 5, 2011.
62. GOG-126Q, Miller DS, Blessing JA, Krasner C, Mannel R, Hanjani P, Pearl ML, Waggoner S, Boardman CH. Phase II evaluation of pemetrexed in the treatment of recurrent or persistent platinum-resistant ovarian or primary peritoneal carcinoma: A study of the Gynecologic Oncology Group. *J Clin Oncol* 27(16): 2686-91, 2009.
63. GOG-186H, Cohn DE, Sill MW, Walker JL, O'Malley D, Nagel CI, Rutledge TL, Bradley W, Richardson DL, Moxley KM, Aghajanian C. Randomized phase IIB evaluation of weekly paclitaxel versus weekly paclitaxel with oncolytic reovirus (Reolysin) in recurrent ovarian, tubal, or peritoneal cancer: An NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol.* 146(3):477-483, 2017.
64. Richardson DL, Sill MW, Coleman RL, et al. Paclitaxel With and Without Pazopanib for Persistent or Recurrent Ovarian Cancer: A Randomized Clinical Trial. *JAMA Oncol.* 2018;4(2):196-202. doi:10.1001/jamaoncol.2017.4218
65. GOG-186K, Matulonis UA, Sill MW, Makker V, Mutch DG, Carlson JW, Darus CJ, Mannel RS, Bender DP, Crane EK, Aghajanian C. A randomized phase II study of cabozantinib versus weekly paclitaxel in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer: An NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol.* 152(3):548-553, 2019.
66. GOG-186G, Richardson DL, Sill MW, Coleman RL, Sood AK, Pearl ML, Kehoe SM, Carney ME, Hanjani P, Van Le L, Zhou XC, Alvarez Secord A, Gray HJ, Landrum LM, Lankes HA, Hu W, Aghajanian C. Paclitaxel With and Without Pazopanib for Persistent or Recurrent Ovarian Cancer: A Randomized Clinical Trial. *JAMA Oncol.* 4(2):196-202, 2018.
67. GOG-186I, Tewari KS, Sill MW, Coleman RL, Aghajanian C, Mannel R, DiSilvestro PA, Powell M, Randall LM, Farley J, Rubin SC, Monk BJ. Bevacizumab plus fosbretabulin in recurrent ovarian cancer: Overall survival and exploratory analyses of a randomized phase II NRG oncology/gynecologic oncology group study. *Gynecol Oncol.* 159(1):79-87, 2020.
68. GOG260, Monk BJ, Kauderer JT, Moxley KM, et al: A phase II evaluation of elesclomol sodium and weekly

paclitaxel in the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube or primary peritoneal cancer: An NRG oncology/gynecologic oncology group study. *Gynecologic Oncology* 151:422-427, 2018

69. GOG9925, Monk BJ, Facchiabene A, Brady WE, Aghajanian CA, Fracasso PM, Walker JL, Lankes HA, Manjarrez KL, Danet-Desnoyers GH, Bell-McGuinn KM, McCourt CK, Malykhin A, Hershberg RM, Coukos G. Integrative Development of a TLR8 Agonist for Ovarian Cancer Chemoimmunotherapy. *Clin Cancer Res.* 2017 Apr 15;23(8):1955-1966.
70. GOG-170D, Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JL. Phase II trial of Bevacizumab in persistent or re-current epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 25(33): 5165-71, 2007.
71. GOG-218, Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, Mannel RS, Homesley HD, Fowler J, Greer BE, Boente MP, Birrer MJ, Liang SX, Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer, a GOG study. *N Engl J Med* 365: 2473-83, 2011.
72. NRG-GY003, Zamarin D, Burger RA, Sill MW, Powell DJ Jr, Lankes HA, Feldman MD, Zivanovic O, Gunderson C, Ko E, Mathews C, Sharma S, Hagemann AR, Khleif S, Aghajanian C. Randomized Phase II Trial of Nivolumab Versus Nivolumab and Ipilimumab for Recurrent or Persistent Ovarian Cancer: An NRG Oncology Study. *J Clin Oncol.* 38(16):1814-1823, 2020.
73. NRG GY001, Konstantinopoulos PA, Brady WE, Farley J, Armstrong A, Uyar DS, Gershenson DM. Phase II study of single-agent cabozantinib in patients with recurrent clear cell ovarian, primary peritoneal or fallopian tube cancer (NRG-GY001). *Gynecol Oncol.* 150(1):9-13, 2018.
74. Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, Mannel R, Shahin MS, Cantuaria GH, Girda E, Mathews C, Kavecansky J, Leath CA III, Gien LT, Hinchcliff EM, Lele SB, Landrum LM, Backes F, O'Ceirbhail RE, Al Baghdadi T, Hill EK, Thaker PH, John VS, Welch S, Fader AN, Powell MA, Aghajanian C. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. *N Engl J Med.* 2023 Mar 27. doi: 10.1056/NEJMoa2302312.

Additional References (Not Cited)

GOG-87L, Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: A Gynecologic Oncology Group phase II trial. *Gynecol Oncol* 109(3): 329- 34, 2008

GOG-127L, Muggia FM, Blessing JA, Method M, Miller DS, Johnson GA, Lee RB, Menzin A. Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study. *Gynecol Oncol.* 92(2): 639-43, 2004.

GOG-127K, Schilder R, Blessing JA, Morgan M, Mangan C, Rader JS. Evaluation of gemcitabine in patients with squamous cell carcinoma of the cervix: A phase II study of the Gynecologic Oncology Group. *Gynecol Oncol.* 76(2): 204-207, 2000.

GOG-127W, Kunos C, Deng W, Dawson D, Lea JS, Zanotti KM, Gray HJ, Bender DP, Guaglianone PP, Carter JS, Moore KN. A phase I-II evaluation of veliparib (NSC #737664), topotecan, and filgrastim or pegfilgrastim in the treatment of persistent or recurrent carcinoma of the uterine cervix: an NRG Oncology/Gynecologic Oncology Group Study. *Int J Gynecol Cancer.* 2015 Mar;25(3):484-92.

GOG-227G, Chan JK, Deng W, Higgins RV, Tewari KS, Bonebrake AJ, Hicks M, Gaillard S, Ramirez PT, Chafe W, Monk BJ, Aghajanian C. A phase II evaluation of brivanib in the treatment of persistent or recurrent carcinoma of the cervix: An NRG Oncology/Gynecologic Oncology Group study.

GOG-229B, McMeekin DS, Sill MW, Benbrook D, Darcy KM, Stearns-Kurosawa DJ, Eaton L, Yamada SD. A phase II trial of thalidomide in patients with persistent or recurrent endometrial cancer with translational research: a Gynecologic Oncology Group study. *Gynecol Oncol.* 105(2): 508-16, 2007.

GOG-229F, Coleman RL, Sill MW, Lankes HA, Nickles Fader A, Finkler NJ, Hoffman JS, Rose PG, Sutton GP, Drescher CW, McMeekin DS, Hu W, Deavers M, Godwin AK, Alpaugh K, Sood AK. A phase II evaluation of aflibercept in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 127(3): 538-43, 2012.

GOG-229G, Alvarez EA, Brady WE, Walker JL, Rotmensch J, Zhou XC, Kendrick JE, Yamada SD, Schilder JM, Cohn D, Harrison CR, Moore K, Aghajanian C. Phase II trial of combination bevacizumab and temsirolimus in the

treatment of recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 129(1): 22-7, 2013.

GOG-229H, Coleman RL, Sill MW, Thaker PH, Bender DP, Street D, McGuire WP, Johnston CM, Rotmensch J. A phase II evaluation of selumetinib (AZD6244, ARRY-142886), a selective MEK-1/2 inhibitor in the treatment of recurrent or persistent endometrial cancer: An NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol*. 2015 Jul;138(1):30-5.

GOG-229I, Powell MA, Sill MW, Goodfellow PJ, Benbrook DM, Lankes HA, Leslie KK, Jeske Y, Mannel RS, Spillman MA, Lee PS, Hoffman JS, McMeekin DS, Pollock PM. A phase II trial of brivanib in recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group Study. *Gynecol Oncol*. 2014 Oct; 135(1):38-43.

GOG-229K, Dizon DS, Sill MW, Schilder JM, McGonigle KF, Rahman Z, Miller DS, Mutch DG, Leslie KK. A phase II evaluation of nintedanib (BIBF-1120) in the treatment of recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group Study. *Gynecol Oncol*. 2014 Dec;135(3):441-5.

GOG-229L, Moore KN, Sill MW, Tenney ME, Darus CJ, Griffin D, Werner TL, Rose PG, Behrens R. A phase II trial of trebananib (AMG 386; IND#111071), a selective angiotensin 1/2 neutralizing peptibody, in patients with persistent/recurrent carcinoma of the endometrium: An NRG/Gynecologic Oncology Group trial. *Gynecol Oncol*. 2015 Sep;138(3):513-8.

GOG-229N, Makker V, Filiaci VL, Chen LM, Darus CJ, Kendrick JE, Sutton G, Moxley K, Aghajanian C. Phase II evaluation of dalantercept, a soluble recombinant activin receptor-like kinase 1 (ALK1) receptor fusion protein, for the treatment of recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group Study 0229N. *Gynecol Oncol*. 2015 Jul;138(1):24-9.

GOG-232B, Powell MA, Filiaci VL, Rose PG, Mannel RS, Hanjani P, DeGeest K, Miller BE, Susumu N, Ueland FR. A phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group (GOG) study. *J Clin Oncol* 28(16): 2727-31, 2010.

Landen CN, Buckanovich RJ, Sill M, et al. A phase I/II study of ruxolitinib with frontline neoadjuvant and post-surgical therapy in patients with advanced epithelial ovarian, Fallopian tube, or primary peritoneal cancer. *J Clin Oncol*. 2022;40(suppl 16):5002. doi: 10.1200/JCO.2022.40.16_suppl.5002

Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, Mannel R, Shahin MS, Cantuaria GH, Girda E, Mathews C, Kavecansky J, Leath CA III, Gien LT, Hinchcliff EM, Lele SB, Landrum LM, Backes F, O'Cearbhaill RE, Al Baghdadi T, Hill EK, Thaker PH, John VS, Welch S, Fader AN, Powell MA, Aghajanian C. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. *N Engl J Med*. 2023 Mar 27. doi: 10.1056/NEJMoa2302312.