Chapter 6 |

The GOG Foundation, Inc. Cervical Cancer Trials


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Studies in Early-Stage Cervical Cancer

Preinvasive Disease

Patients with cervical intraepithelial neoplasia (CIN) generally have been treated with local surgical excision. The overall cure rates are high. Early Gynecologic Oncology Group (GOG) investigations in this area consist of GOG 31 and GOG 32, both of which were active between 1978 and 1981. GOG 31 compared local excision to cryosurgery in patients with CIN-I and CIN-II, while GOG 32 compared surgical conization to cryosurgery in patients with CIN-III. Both studies were designed to evaluate morbidity and cost. Neither study could be successfully completed. More recently, GOG 207 evaluated the daily use of celecoxib as a chemo preventive for up to 18 weeks in women with CIN-III in a randomized phase II trial. While celecoxib had a similar rate of histologic progression (40% vs. 34.1%), regression was greater for this agent (47.3% vs. 14.3%) in women with high serum VEGF levels suggesting this may be a predictive biomarker of response to therapy (Rader J et al. *Gyn Onc* 145(2) 2017)

In retrospect, it appears that there were several reasons for the failure of these three studies:

- Access to patients. Some GOG institutions that have adequate numbers of patient referrals with invasive disease but see comparatively few patients with CIN. As such, these patients are managed successfully at the community level by general gynecologists.

- Patient willingness. Some patients declined to be randomized between an outpatient and an inpatient procedure, as in GOG 32. Similarly, although 130 women enrolled in GOG 207, 19 (18.5%) were either not treated, evaluable or lost to follow-up.

- Inability to obtain sufficient follow up. All study populations were difficult to follow because of problems with follow up appointments and compliance. This is characteristic of patients with CIN. Individuals who are in the lower socio-economic strata or have a transient lifestyle have the fewest resources available to them. The data from all three studies have been published.[1,64]

- Baseline rate of regression. Importantly, while high grade CIN is a known pre-malignant condition, regression to lower grade CIN and/or normal histology occurs around 35% of the time and is important when considering study design and finding chemo preventive agents to improve upon this.

Stage IA/IB1 Disease

Stage I accounts for approximately 39% of all cervix cancer patients world-wide and perhaps 60% of previously untreated patients in GOG institutions. There has been only one GOG study conducted for patients with stage IA (early invasive) disease: a surgical pathological study that was active between 1971 and 1976 (GOG 5). Protocol 5 evaluated the characteristics of stage IA, or “microinvasive” cervical carcinoma. These results have contributed to the generally accepted working definition of "microinvasive” cervical cancer used in North America.[2]

In patients with stage IB disease, the GOG conducted a large prospective surgical pathological study (GOG 49) between 1981 and 1984 in which patients underwent an exploratory laparotomy, bilateral pelvic and para-aortic lymph—adenectomy, and if para-aortic nodes were negative on frozen section—radical hysterectomy. There were 1,003 patients entered on this study. The data from this trial underwent intensive analysis to define risk groups that would form the basis for future phase III therapeutic trials. Pre-operative clinical factors that were evaluated included:

- Cell Type
- Histologic Grade
- Patient Age
- Performance Status
- Maximum Clinical Tumor Diameter
- Gross Description of the Neoplasm
- Number of Quadrants Involved

Post-operative pathologic factors analyzed included:

- Pelvic and Para-Aortic Node Status
- Space Involvement
- Depth of Invasion
- Parametrial Extension
- Uterine Extension
- Positive Pelvic Washings
- Surgical Margin Status

The pathologic risk factors defined by the GOG in Protocol 49 were then used to determine the need for post-operative therapy. Even in the absence of nodal metastases, patients with large tumors, deep stromal invasion, or capillary-lymphatic space (CLS) involvement were shown to be at risk for tumor relapse and death.[3,4] This analysis provided the database on which subsequent GOG studies of stage IB disease were based. The results of the study also notably contributed to the understanding of significant prognostic factors in early cervical carcinoma. Patients with stage IB disease who did not have large tumors, deep stromal invasion or capillary-lymphatic space invasion, are adequately treated with either radical operation or radiation, with excellent rates of control and almost always resulting in a cure. Thus, there appears to be little opportunity to improve survival for these patients.

With the background of the database from GOG 49, the GOG identified subsets of Stage IB patients which might benefit from additional therapy. Based on the multivariate analysis of risk factor data from GOG 49, two protocols were developed to examine the role of multimodal therapy in patients with Stage IB disease and unfavorable prognostic features. A randomized phase III study (GOG 92) examined the role of adjuvant pelvic radiation therapy in patients with Stage IB disease, who are found to have intermediate risk factors such as CLS involvement, deep invasion of the cervical stroma, and lesion size. Patients were randomized after radical hysterectomy and pelvic lymphadenectomy to receive either no adjuvant therapy versus pelvic radiation therapy. This trial was designed to answer a question that had been debated in gynecologic oncology for years. Open from March 1988 to August 1993, this trial determined that the addition of radiation improved local control and progression-free survival; however, there were increased adverse effects observed in the irradiated group.[5] An update of the results of this clinical trial were published in 2006, con- firming the long-term benefits of adjuvant radiation in the setting of "intermediate risk factors" following radical hysterectomy. Interestingly, this post-hoc analysis suggested that pelvic radiation appeared to be particularly beneficial for patients with adenocar cinoma or adenosquamous histologies.[6]

In 2010, the GOG, in collaboration with Korean GOG, activated GOG 263 (ClinicalTrials.gov Identifier: NCT01101451). This randomized phase III trial is set to enroll 360 subjects and investigates the role of adding weekly IV cisplatin to these "GOG 92-like" patients with post-operative "intermediate risk factors."

Post-operative pelvic radiation therapy has become standard therapy for patients with occult parametrial extension. Though much has been written on this subject, these patients are uncommon and represent a varied population. GOG 109 was performed as an intergroup study with the Southwest Oncology Group (SWOG). Opened to patient entry in October 1990, this phase III trial evaluated post-operative pelvic radiation therapy following radical hysterectomy with versus without cisplatin and infusion 5-FU to determine if concurrent chemotherapy improved local control and survival.[7] This study was reported after the three studies in locally- advanced disease (see below) and the ensuing NCI Clinical Alert confirmed that the benefits of chemoradiation extended to these patients as well. This study has also been updated. A post-hoc hypothesis generating analysis suggested that the prognostic significance of histological type, tumor size, number of positive nodes, and parametrial extension in the radiation alone group was less apparent when chemotherapy was added. The absolute improvement in five-year survival for adjuvant chemotherapy and radiation in patients with tumors < or =2 cm was only 5% (77% versus 82%), while for those with tumors >2 cm it was

19% (58% versus 77%). Similarly, the absolute five-year survival benefit was less evident among patients with one nodal metastasis (79% versus 83%) than when at least two nodes were positive (55% versus 75%).[8]

Moving forward, as the potential benefits of chemotherapy in treating cervical cancer become more apparent, additional cycles of adjuvant chemotherapy are being investigated (also see GOG 274 below). GOG 0724 (ClinicalTrials.gov Identifier: NCT00980954) is a collaboration between the GOG and the RTOG. This study opened in 2009 seeking to enroll 285 subjects. Patients with "high risk factors" similar to those treated on GOG 109 are randomized to either standard external beam radiation or intensity modulated radiation therapy to the pelvis once daily five days a week for 5-6 weeks with concurrent IV cisplatin weekly for six weeks versus the same regimen along with additional four cycles of IV paclitaxel and carboplatin every 21 days. The results of this as well as GOG 263 are eagerly awaited.

FIGO 2018 Stage IB3 Disease

Patients with bulky stage IB disease (> 4 cm), or barrel shaped tumors, are considered by some to be poor candidates for primary radical hysterectomy. GOG 71 was a randomized phase III trial which compared radiation therapy with and without adjuvant ex trafascial hysterectomy. This trial was based on published data suggesting that adjuvant surgery in this patient group was beneficial. Opened in late 1984, this trial accrued patients very slowly at first. The study subsequently accrued patients well and reached its accrual goal in 1991. The combination of radiation followed by operation had an advantage over radiation alone with respect to local (central pelvic) tumor control. This protocolrm follow- up, however, there was no survival advantage observed for the group who underwent hysterectomy after radiation therapy.[9] This protocol represents one of the few studies comparing single modality to combined modality therapy in this patient population.

When the GOG was ready to proceed to the next trial, only the data on local control were mature; thus, the GOG retained adjuvant hysterectomy in the next study in this population. GOG 123 opened in February 1992. This phase III trial compared pelvic radiation therapy followed by extra-fascial hysterectomy with and without weekly cisplatin to determine if cisplatin improved local control or survival.[10] This report accompanied two other trials in prompting an NCI Clinical Alert and changing the standard of care in this patient population.

A pilot study (GOG 89-03) evaluated an accelerated course of neoadjuvant cisplatin and vincristine prior to radical hysterectomy in therapy-naïve patients with suboptimal stage IB2 cervical carcinoma to determine the response rate of this regimen. There were 35 patients accrued. The response rate was high (~85%) and this regimen was incorporated as the study regimen of GOG 141. The study opened to patient entry in August 1993. This phase III trial compared radical hysterectomy alone to the same operation following an accelerated course of cisplatin and vincristine and failed to show any additional objective benefit to the added neoadjuvant chemotherapy. Survival and operability were not improved, and the use of postoperative adjuvant radiation did not decrease.[11]

Pretreatment Surgical Staging

The GOG undertook a careful prospective evaluation of surgical staging for locally advanced cervical cancer (GOG 19). Between November 1973 and June 1976, there were 290 evaluable patients who underwent surgical staging (para-aortic lymphadenectomy). It was confirmed that clinical staging underestimated the true extent of disease in a large number of patients (Table 1).

Table 1.

Clinical Stage	# Patients	% Upstaged	% with + PA nodes
IB	143	24%	6%
II	80	52%	29%
III	63	45%	30%
IV	4	50%	33%

There were, however, added surgical adverse effects as well as the additional complications of radiation after operative manipulation.[12] Following up on this demonstrated inaccuracy of clinical staging, the GOG conducted a prospective evaluation of imaging of the para-aortic nodes. From October 1982 to February 1988, 264 eligible and evaluable patients with stages IIB-IVA disease underwent CT scan, ultrasound and lymphangiogram, followed by surgical staging. There were 64 patients (24%) with confirmed positive PA nodes. Both CT and ultrasound had a very high negative predictive value, but low sensitivity. Lymphangiogram had the highest sensitivity (79%).[13] In addition, a non-randomized comparison (GOG 24) of extraperitoneal and transperitoneal surgical staging procedures showed similar accuracy and similar intraoperative complications. However, the extraperitoneal approach was associated with a lower frequency of post irradiation regional enteric complications and has since been the preferred method of surgical staging.[14]

Interestingly, with recent advances in body imaging, including widespread use of positron emission tomography with fluorine-18 fluorodeoxyglucose (FDG-PET/CT), surgical staging has been largely abandoned in routine clinical practice.[15] However, a retrospective GOG analysis of GOG 85, GOG 120 and GOG 165 showed an improved four-year survival rate (54.3% vs 40%) among patients with locally advanced cervical cancer treated with chemotherapy and radiation after surgical evaluation of the para- aortic lymph nodes,[16] compared to negative imaging (mostly CT) alone. In collaboration with ACRIN, GOG 233 was a prospective evaluation of preoperative FDG-PET/CT scanning prior to primary chemoradiation therapy to detect retroperitoneal lymph node metastasis in participants with locoregionally advanced carcinoma of the cervix (ClinicalTrials.gov Identifier: NCT00416455).[65] Of one hundred sixty-nine accrued patients with locally advanced cervical cancer, 153 underwent a diagnostic contrast enhanced CT in conjunction with their PET to identify potential nodal involvement and had pathologic specimens for assessment. Following imaging, patients underwent either a laparoscopic or extraperitoneal lymphadenectomy with assessment of bilateral obturator, external iliac, common iliac and para-aortic lymph node dissection. Sensitivity and specificity were calculated and varied by anatomic location. While overall both sensitivity (0.81 vs. 0.77; p=0.17) as well as specificity (0.69 vs. 0.63; p=0.32) favor PET imaging, sensitivity was greatest in the pelvis (0.83 vs. 0.79; p=0.15) while specificity was more heterogenous with CT alone seemingly superior for the abdomen (0.85 v. 0.89; p=0.21) and essentially equivalent for the pelvis (0.63 vs. 0.62; p=0.83).

Studies in Advanced Cervical Cancer

GOG research in cervical cancer is broad based and constantly evolving over time. It encompasses a spectrum of clinical studies, from phase I to phase III, on the treatment of advanced disease; subset analyses of the large phase III randomized trials have generated hypotheses to be tested in subsequent trials. Ongoing translational research accompanying the randomized phase III studies leads to exploration of new strategies in future randomized trials. Completed studies also have delineated tumor and treatment-related prognostic and predictive factors for outcomes in relation to specific therapeutic interventions. The GOG research in advanced cervical cancer has contributed significantly to broad and international acceptance of concurrent chemotherapy and radiation as the standard of care in advanced disease.

Approaches to Locally Advanced Cervical Cancer: Earlier GOG Investigations

In 1979, the GOG was pioneering in its exploration and reporting of various treatment strategies which combined treatment concurrent with radiation. The first evidence of benefit to this strategy resulted from a phase III study (GOG 4) in which the role of concurrent hydroxyurea versus placebo with pelvic radiation was examined in the treatment of stage IIIB and IV cervical cancer.[17] Studies in this early era of group-wide research were not necessarily statistically powered and designed as they are currently. However, this study demonstrated that although the use of hydroxyurea was accompanied by increased toxicity over radiation alone, it led to apparent improvements in progression-free and overall survival. Concurrent hydroxyurea became a standard in the GOG to which other concurrent chemotherapy would be compared in future trials. Another innovative study (GOG 24), reported in 1986, examined the role of a nonspecific immune stimulant, Corynebacterium parvum, as concurrent and adjuvant therapy to standard pelvic irradiation. Improved outcomes in advanced cervical cancer were not achieved.[18]

Subsequent studies of the GOG became more rigorous in their design, were more carefully conducted, and statistical methods for analysis became more sophisticated. Pursuant to ongoing studies of concurrent therapies with radiation, the GOG performed the first study of a "targeted therapy." Concurrent hydroxyurea was compared to the use of concurrent misonidazole, a hypoxic cell radiosensitizer. Given the fact that hypoxic cells are known to be present in a majority of cervix cancers and their presence causes relative radiation resistance, this was a rational targeting strategy to explore. The results of this trial (GOG 56) demonstrated that misonidazole in tolerable doses did not improve outcomes over those using concurrent hydroxyurea and radiation.[19]

Ancillary data analyses of the large phase III trials have contributed significantly to our understanding of advanced cervical cancer. A multivariate analysis of prognostic variables in the three previous trials (GOG 24/56/59) of concurrent therapies with radiation demonstrated that patient age, performance status, paraaortic lymph node status, tumor size and pelvic node status were all significantly associated with progression-free survival; in addition to the FIGO stage, bilateral parametrial extension or sidewall disease were also significant factors.[20] Such analyses allow stratification of patients into groups with varying risks, thus contributing to future trial design, conduct and analyses.

Chemoradiation Therapy: 1999 NCI Clinical Alert

In pursuit of identification of more effective concurrent therapy regimens, the GOG has sequentially examined a

number of agents in differing regimens (Table 2).

Table 2. Randomized GOG Studies in Locally Advanced Cervical Cancer.

1971

- Protocol 004 (1971-1976) - RT + Placebo vs. RT + H
- Protocol 024 (1977-1981) - RT vs. RT + C. Parvum
- Protocol 056 (1981-1985) - RT + H vs. RT + Misonidozole
- Protocol 085 (1986-1990) - RT + H vs. RT + CDDP + 5FU
- Protocol 120 (1992-1997) - RT + H vs. RT + CDDP vs. RT + 5FU + CDDP + H
- Protocol 165 (1997-2000) - RT + CDDP vs. RT + PVI 5FU
- Protocol 191 (2001-2003) - RT + CDDP vs. RT + CDDP + Hgb support
- Protocol 219 (2005-2009) - RT + CDDP vs. RT + CDDP + TPZ
- OUTBACK (0274) (2011-2017) - RT + CDDP vs. RT + CDDP + 4 cycles of Carboplatin/Paclitaxel
- NRG-GY006 (2016-present) – RT + CDDP vs. RT + CDDP + Triapine
- GOG 3047/ENGOT cx11/KEYNOTE A18 (2018-present)- RT + CDDP +/- Pembrolizumab
- GOG 3092/ENGOT cx--/eVOLVE (2023-present)-RT + CDDP +/- Volrustomig (anti-PD1/CTLA4 bispecific)

2023

These agents were selected because in vitro and in vivo trials demonstrated a positive interaction when they were used in conjunction with radiation. These trials were conducted in the adjuvant therapy setting in earlier disease (GOG 109)7, as definitive treatment in stage IB2 (FIGO 2009) cervical cancer (GOG 123)10, and in surgically staged patients with negative para-aortic nodes stage IIB- IVA (GOG 85 and GOG 120).[21,22] These studies in conjunction with an intergroup study with the RTOG[23] showed such an important, positive impact on progression-free survival, overall survival, and local control for patients with advanced cervical cancer that the results stimulated a rare NCI Clinical Alert suggesting that all patients receiving radiation for cervical cancer should be considered for receiving cisplatin-based chemotherapy concurrently with their radiation treatment.[24] These studies demonstrated absolute improvements in survival of 8-18%, and a very consistent risk reduction in death due to disease of approximately 40%. The first randomized trial (GOG 85) in advanced disease compared a combination of cisplatin and 5FU every 21 days versus hydroxyurea, and demonstrated better progression-free and overall survival for the 5FU/cisplatin arm.21 Following a phase I study (GOG 113) to define the tolerability of the three-drug combination of hydroxyurea, 5FU and cisplatin,[25] a subsequent three-arm randomized trial com- pared the results of the "standard" of hydroxyurea and radiation to the three-drug combination concurrent with radiation, and to a more simple regimen of weekly cisplatin 40 mg/m2 (total maximum dose of 70mg) and radiation as used in the positive trial (GOG 123) in stage IB2 cervical cancer.[10] This important and definitive three-arm study (GOG 120) demonstrated an improvement in progression-free and overall survival for the three-drug combi nation and the single-agent weekly cisplatin compared to hydroxyurea.[22] Because there was significant grade III and IV toxicity associated with the three-drug combination, the conclusion was drawn that weekly cisplatin offered the best therapeutic ratio for a concurrent chemoradiation scheme. Weekly concurrent cisplatin at 40 mg/m2 (total maximum dose of 70mg) with radiation appears to be the regimen of choice and is now accepted internationally. The weekly cisplatin regimen, however, has never been directly compared to combinations of 5FU and platinum. However, the GOG conducted another randomized trial comparing a protracted venous infusion of 5FU versus the weekly cisplatin regimen (GOG 165). This study was prematurely closed at a planned interim analysis because there was a statistical demonstration that the 5FU would never yield improved results over those of weekly cisplatin alone.[26]

In pursuit of even more effective concurrent regimens with radiation in the management of advanced dis- ease and in pursuit of more specifically targeted therapies, the current study of the GOG in stage IB2-IVA disease compares the combination of tirapazamine, a specific hypoxic cell cytotoxin, plus cisplatin and radiation versus a standard weekly cisplatin and radiation alone. Although the design of this study acknowledges that tumor hypoxia remains a significant problem limiting local control and survival in cervical cancer since hypoxia causes both chemo and radiation resistance and stimulates angiogenic pathways and tumor growth, it did not show any improvement in PFS or OS .[66] Specifically, the OS was nearly identical for the control arm, 70.6%, as compared to the experimental with tirapazamine, 70.5% (unadjusted HR 10.42, 95% CI 0.71-1.53, p=0.8333) and the trial was unable to complete the planned accrual secondary

to the lack of availability of the investigational agent.

More recently the GOG completed participation in a worldwide study investigating the impact of additional cycles of chemotherapy following definitive cisplatin concurrent with pelvic radiation. Led by the Australia New Zealand Gynaecological Oncology Group (ANZ- GOG), GOG 274, otherwise known as the OUTBACK trial, is a randomized phase III trial of cisplatin and radiation therapy together with or without carboplatin and paclitaxel among patients with locally advanced cervical cancer. This trial opened in 2012 and although scheduled to enroll 780 subjects, was amended to enroll approximately 900 patients following consultation with the data safety monitoring committee secondary to a higher-than-expected lack of chemotherapy commencement as well as a lower-than-expected event rate (ClinicalTrials.gov Identifier: NCT01414608). Ultimately, 926 women were randomized between the two treatment arms (461 for chemoradiation alone and 465 for chemoradiation followed by adjuvant chemotherapy) with ECOG PS=0, squamous cell carcinoma histology, Stage IIB disease and approximately a 50% pelvic nodal involvement rate among the most common clinicopathologic factors. Factors associated with successful completion of chemoradiation including the number of cycles of cisplatin administered (four or five), performance of external beam radiotherapy without a break, administration of brachytherapy and completion of radiation treatment within eight weeks were similar between both arms. Although the majority of patients (361 of 463, 78.0%) randomized to adjuvant paclitaxel and carboplatin chemotherapy commenced this therapy, a substantial proportion in fact did not. Moreover, only 285 women completed the 4 cycles of protocol directed chemotherapy. With a median follow-up of 60 months, unfortunately, OS was similar for the experimental group with adjuvant chemotherapy 72% as compared to the control 71% (HR 0.90: 95% CI 0.70-1.17, p =0.8). The low event rate in the control arm underscores the favorable outcomes that evolved in the platinum + RT era.

Triapine, a novel ribonucleotide reductase inhibitor, was previously evaluated in an NCI sponsored phase I trial and achieved study endpoints for further development. Based on these exciting early phase results, NRG-GY006 was initially designed as a randomized phase II trial evaluating the addition of thrice weekly triapine to the standard cisplatin chemoradiation backbone before being modified to a randomized phase III registration trial. In addition, GY006 is evaluating the role of IMRT in primary treatment of locally advanced cervical cancer, the impact of knowledge-based planning on radiation plans, as well as the proportion of women with a complete metabolic response on a post-treatment PET/CT (ClinicalTrials.gov Identifier: NCT02595879). Enrollment concluded in 2022 and results are pending.

The GOG has recognized as have others that a subset of patients with cervical cancer metastatic to para-aortic nodes may be cured with radiation alone. Attempts to improve cure rates in this group of patients resulted in an observational study (GOG 125) in which concurrent 5FU plus cisplatin chemotherapy was added to extended field radiation to encompass the pelvis and para-aortic nodes.[27] This study demonstrated that a tolerable concurrent chemotherapy regimen could be given with extended field irradiation. The hypothesis generated is that some advantage may accrue to the addition of chemotherapy to radiation over radiation alone, although no study comparing these two regimens directly has been conducted in this patient group. During the evolution of the multiple phase III studies of the GOG in advanced cervical cancer, important modifications have been made over time in radiation treatment protocols of the GOG. The GOG accepted that a large body of observational data supports that brachytherapy using high-dose rate (HDR) has a similar therapeutic ratio to low-dose rate brachytherapy (LDR), i.e., local control and treatment complications are comparable. The GOG now allows use of either HDR or LDR in its protocols for the treatment of advanced disease. This allows broader trial participation as LDR declines in usage. In addition, the importance of other radiation factors such as treatment time and tumor volume have been recognized by the GOG; strict limitations have been placed on acceptable overall treatment times for radical pelvic irradiation (eight weeks). Adequate pelvic radiation volumes aided by CT or MRI tumor delineation better encompass disease particularly posteriorly in the pelvis. Ancillary data analyses in the study of Lanciano et al (GOG 165) has clearly identified that cigarette smoking is an independent predictor for significantly worse outcome in patients being treated with locally advanced cervical cancer.[28]

In summary, 50 years of GOG multidisciplinary research in locally advanced cervical cancer has markedly influenced the worldwide management of patients and has resulted in significant improvement in patient survival,[29] though the standard of platinum and RT set in 1999 remains the standard in 2023. Attempts to improve survival beyond GOG 120 have yet to prove successful, but the curative opportunity in this setting maintains progress as a high priority. Current studies are focused on the addition of immune checkpoint inhibitors to cisplatin-RT and as post-treatment maintenance (see im-

munotherapy section).

Chemotherapy for Advanced, Recurrent, Metastatic Cervical Carcinoma

When cervical cancer cannot be treated with surgery and/or radiation therapy with curative intent, the prognosis has historically been poor. However, major advances in systemic therapy have led to marked improvements in this setting. The need to identify an effective chemotherapy for these patients has been one of the primary goals of the Cervix Committees for four decades and is yet another area where only the GOG has been able to advance clinical science. Only through the conduct of well-designed phase III studies may the merits of drugs or combinations be evaluated, compared, and discarded versus selected for further study and community adoption.

Platinum Compounds

Because of its recognized activity against other solid tumors, the GOG initiated a phase II study of cisplatin 50 mg/m2 at an infusion rate of 1 mg/min every three weeks in patients with stage IVB or recurrent cervical cancer. Among the 22 patients who had not received prior chemotherapy, the response rate was 50% (3 CR, 8 PR). The response rate was 17% (0 CR, 2 PR) in the group of 12 patients who had received prior chemotherapy.[30] Although later series with larger patient numbers reported lower response rates, generally in the 20-30% range, the activity of cisplatin was confirmed. To further explore the use of cisplatin in the treatment of cervical carcinoma the GOG conducted a study of cisplatin at three dose schedules to determine if improved results could be achieved through increased dose intensity. There were 581 women entered on this trial and 497 were considered evaluable. Although the objective response rate increased from 21% to 31% (p = .015) by increasing the cisplatin dose from 50 mg/m2 to 100 mg/m2 every three weeks, there was no associated improvement in the complete response rate, progression-free interval or overall survival; furthermore, higher cisplatin doses were associated with greater nephrotoxicity and myelosuppression.[31] In a subsequent GOG study, 380 patients were randomized to receive 50 mg/m2 cisplatin given as a short (1 mg/min) versus 24-hour infusion. The overall response rate was essentially identical (18%) in each group. Although GI toxicity (nausea and emesis) was lower in the prolonged infusion group, the incidence of other adverse effects—nephrotoxicity, myelosuppression, neurotoxicity—did not differ.[32]

Recognizing the activity and associated toxicity profile of cisplatin, the GOG initiated a randomized phase II study of the platinum analogs carboplatin and iproplatin. Clinical experience indicated minimal nephrotoxicity or neurotoxicity, and both drugs could be administered in an outpatient setting without prior hydration. The study was conducted from July 1984 through July 1987, and 394 patients were entered. The starting dose of carboplatin (400 mg/m2) was reduced to 340 mg/m2 in patients who had received prior radiation therapy. Similarly, the starting dose of iproplatin (270 mg/m2) was reduced to 230 mg/m2 doses in previously irradiated patients. Both treatments were repeated every 28 days. The objective response rates were 15% for carboplatin and 11% for iproplatin. Although the study was not designed to compare either analog to cisplatin, these response rates were lower than what had been reported for cisplatin. Furthermore, after treatment failure there were several patients who subsequently went on to receive cisplatin. For 22 of these patients, follow-up data were available, and the secondary response rate to cisplatin (18%) was higher than the primary response rate to either analog. The GOG concluded that "...this finding seems to be further evidence that cisplatin must remain the drug of choice for advanced squamous cell cancer of the cervix."[33]

The Development of Cisplatin Combinations

Given the modest activity of cisplatin and consequent lack of a meaningful impact on survival, the GOG strove to identify other drugs that were either more effective than or could be used in combination with cisplatin. These studies represented an effective collaboration between Developmental Therapeutics and the Cervix Committee. Several agents were studied and proven inactive. However, the GOG conducted a phase II study of mitolactol (di- bromodulcitol or DBD) and reported a 29% response rate.[34] Other phase II studies—conducted both by GOG and other groups— identified ifosfamide as an active agent with response rates ranging from 16-40%.[35-37] After subsequent phase I studies determined the feasibility of administering these agents in combination with cisplatin, the GOG conducted a phase III trial (GOG 110) of cisplatin versus cisplatin plus DBD versus cisplatin plus ifosfamide (Table 3). Compared to cisplatin alone, cisplatin plus ifos famide had a significantly higher response rate (33% versus 19%) and progression-free interval (4.6 versus 3.2 months) with no significant improvement in survival. Furthermore, adverse side effects were significantly higher in the ifosfamide-containing arm. Peripheral and central neurotoxicity were more frequent and more severe with cisplatin plus ifosfamide versus cisplatin alone. CNS toxicity ranged from confusion to somnolence to coma and/or seizures. There were two treatment-related deaths in patients receiving cisplatin plus ifosfamide: one patient had a cardiorespira-

Table 3. Platinum-Based Phase III GOG Studies in Recurrent and Metastatic Cervical Cancer.

Study	Agent	RR	OS
43 (1987)	CDDP 50 mg/m^2	21%	
(n=497)[1]	CDDP 100 mg/m^2	31%	7.1 mos
	CDDP 20 mg/m^2 x 5d	25%	
64 (1989)	Rapid CDDP	18%	6.2 mos
(n=331)[2]	24 hr CDDP	18%	
77 (1989)	Carboplatin	15%	6.2 mos
(n=394)[3]	Iproplatin	11%	

[1] Bonomi, P. et al; *J Clin Oncol*, 1985, 3: 1079-85.
[2] Thigpen, JT et al; *Gyneol Oncol*, 1989; 32: 198-202.
[3] McGuire III, WP et al; *J Clin Oncol*, 1989; 7: 1462-8.

Table 4. Platinum-Combination Phase III GOG Studies in Recurrent and Metastatic Cervical Cancer.

Study	Agent(s)	RR	OS
110 (1997)	CDDP	18%	8.0 mos
(n=454)[1]	CDDP/MTL	21%	7.3 mos
	CDDP/IFEX	31%	8.3 mos
149 (2002)	CDDP/IFEX	32%	8.4 mos
(n=287)[2]	CDDP/IFEX/BLEO	31%	8.5 mos

[1] Omura, GA et al, *J Cline Oncol*, 1997; 15: 165-71.
[2] Bloss, JD et al, *J Clin Oncol*, 2002; 20: 1832-7.

tory arrest while comatose and the other developed renal failure and refused dialysis. The eligibility criteria for the study were modified to include only patients with serum albumin > 3.0 g/dL and serum creatinine within normal limits for the institution. Patients with bilateral hydronephrosis were made ineligible. There were no further cases of fatal CNS toxicity, but lesser degrees of encephalopathy were still observed in patients receiving cisplatin plus ifosfamide.[38]

Several studies had suggested the addition of bleomycin to the combination of cisplatin plus ifosfamide yielded higher response rates and may also improve survival. The GOG initiated a phase III study comparing the combination of cisplatin plus ifosfamide with versus without bleomycin (Table 4). These regimens proved essentially identical in terms of objective response rates (approximately 32%), progression-free survival, and overall survival.[39]

GOG Protocols 169 and 179

Discordant results from GOG protocol 110 (improved response rates and progression-free survival versus increased toxicity and no improvement in overall survival) combined with increasing expertise in the group to assess quality of life, prompted a fundamental change in the design of future prospective trials in patients with recurrent/metastatic cervical cancer. Patient-reported quality of life was deemed an essential study endpoint in this patient population with poor median survival. These ultimately successful endeavors were the result of an effective collaboration between the Cervix Committee and the expertise of the Quality of Life Committee.

The first randomized controlled study of palliative chemotherapy in cervical cancer to prospectively obtain quality of life measurements, in addition to traditional clinical outcomes measures, was the phase III trial (GOG 169) of cisplatin plus paclitaxel versus cisplatin. The GOG had previously reported a 17% response rate for paclitaxel against advanced squamous cell carcinoma of the cervix.[40] The combination of cisplatin and paclitaxel was subsequently evaluated in a phase II study. Among the 47 patients enrolled in the study, there were 41 evaluable for response (and 40 had received prior radiation therapy). The most frequent dose-limiting toxicity was neutropenia and two patients died from neutropenic sepsis. There were 19 patients who responded to treatment, including five complete responders, for an objective response rate of 46%.[41] There were 264 eligible patients randomized on GOG 169. Objective response rates were 19% (6% CR, 13% PR) for cisplatin versus 36% (15% CR, 21% PR) for cisplatin plus paclitaxel (p = .002). The median progression-free survival was also improved with the addition of paclitaxel, but overall survival was not improved (8.7 months for cisplatin versus 9.7 months for cisplatin plus paclitaxel). Although toxicity, particularly myelosuppression, was more common in the group of patients receiving paclitaxel, this did not result in worsening quality of life.[42]

A GOG phase II study identified topotecan as a drug with significant activity against cervical carcinoma.[43] In vitro studies showed that topotecan and cisplatin are synergistic.[44] According to studies conducted by the North Central Cancer Treatment Group (NCCTG), the MVAC (methotrexate plus vinblastine plus doxorubicin plus cisplatin) regimen yielded a 66% response rate in 19 patients with advanced/recurrent cervical cancer with a median overall survival of 11.5 months. Three patients survived more than three years.[45] Other investigators also reported objective tumor responses in more than half of patients with MVAC chemotherapy.[46,47] The GOG initiated a phase III trial (GOG 179) comparing cisplatin

Table 5.

Protocol	Regimen	#Pts	OR	CR	PFS (mos)	OS (mos)
GOG 110	P	140	19%	6%	3.2	8.0
	P + IFX	151	31%	13%	4.6	8.3
GOG 169	P	134	19%	6%	3.0	8.9
	P + T	130	36%	15%	4.9	9.9
GOG 179	P	145	13%	3%	2.9	7.0
	P + Topo	148	26%	10%	4.6	9.2

versus cisplatin plus topotecan versus MVAC, again with quality of life included among the outcomes measures. The MVAC arm was closed by the Data Safety Monitoring Board following four treatment-related deaths among 63 patients. There were 293 eligible patients randomized to receive one of the cis- platin-containing regimens. Objective response rates were 13% (3% CR, 10% PR) for cisplatin versus 26% (10% CR, 16% PR) for cisplatin plus topotecan (p = .004).

Although GOG 179 resulted in a statistically significant improvement in overall survival with the cisplatin plus topotecan combi- nation, median survival in this study was not appreciably different than that for the two previous GOG phase III trials (Table 5).

Reasons for this may include an increasing use of concurrent chemotherapy for patients with locally advanced cervical cancer undergoing primary radiation therapy. For example, there was an approximate two-fold increased use of concurrent chemotherapy among patients who received cisplatin plus topotecan on GOG 179 (58%) versus cisplatin plus paclitaxel on GOG 169 (31%) (Table 6).

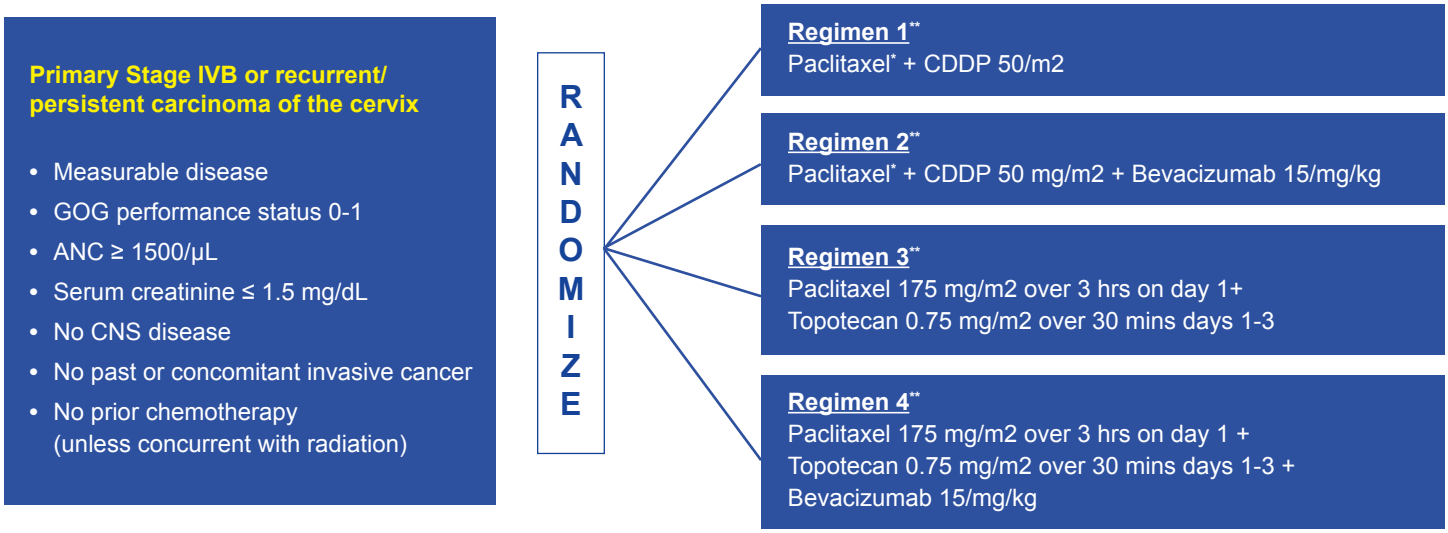
Two prior phase II trials identified vinorelbine as an active agent against cervical carcinoma.[50,51] The GOG conducted a phase II study of cisplatin plus vinorelbine (GOG 76-Z) and reported a response rate of 30% and only mild toxicity.[52] Gemcitabine has been shown to have limited activity against cervical cancer;[53] how- ever, studies have demonstrated synergy between gemcitabine and cisplatin in vitro and in vivo[54] and the combination has been reported to result in response rates of 40 - 95% in small phase II trials in advanced cervix cancer patients.[55-58] As a follow-up to these studies, the GOG initiated a randomized phase III study (GOG 204) of cisplatin plus one of four drugs: paclitaxel (PC), topotecan (TC), vinorelbine (VC), or gemcitabine (GC) in stage IVB, recur- rent or persistent carcinoma of the cervix. A total of 513 patients were enrolled when a planned interim analysis recommended early closure for futility. The experimental-to-PC hazard ratios of death were 1.15 (95% CI, 0.79 to 1.67) for VC, 1.32 (95% CI, 0.91 to 1.92) for GC, and 1.26 (95% CI, 0.86 to 1.82) for TC. The hazard ratios (HRs) for progression-free survival (PFS) were 1.36 (95% CI, 0.97 to 1.90) for VC, 1.39 (95% CI, 0.99 to 1.96) for GC, and 1.27 (95% CI, 0.90 to 1.78) for TC. Response rates (RRs) for PC, VC, GC, and TC were 29.1%, 25.9%, 22.3%, and 23.4%, respectively. The arms were comparable with respect to toxicity except for leucopenia, neutropenia, infection and alopecia. The trend in RR, PFS, and OS favored PC making this the global standard in this setting.[59] Importantly, this was the first study where the median survival for these high-risk patients eclipsed one year. Finally, patient-reported quality of life was not different among the four treatment arms.[60]

The first targeted agent to show activity in treating recurrent cervical cancer was bevacizumab, a humanized monoclonal antibody targeting vascular-endothelial growth factor (VEGF). GOG 227C studied single-agent bevacizumab at 15 mg/kg intravenously every 21 days until disease progression or prohibitive toxicity among women with recurrent cervical cancer who had measurable disease, and a GOG performance status < or = 2. Eleven patients (23.9%; two-sided 90% CI, 14% to 37%) survived progression-free for at least six months, and five patients (10.9%; two-sided 90% CI, 4% to 22%) had partial responses. The median response duration was 6.21 months (range, 2.83 to 8.28 months). The median PFS

Table 6.

GOG Protocol 169	Response Rate	Prior Cisplatin	Median Survival
CDDP	19%	30%	8.8 mos
CDDP/Paclitaxel	36%	24%	9.7 mos
GOG Protocol 179	**Response Rate**	**Prior Cisplatin**	**Median Survival**
CDDP	13%	56%	6.5 mos
CDDP/Topotecan	27%	58%	9.4 mos

Table 7. GOG 240



and overall survival times were 3.40 months (95% CI, 2.53 to 4.53 months) and 7.29 months (95% CI, 6.11 to 10.41 months), respectively.[61] This result was not surprising since an earlier translational companion study of GOG 109 showed the independent prognostic significance of tumor angiogenesis for both PFS and OS in high-risk, early-stage cervical cancer.[62] The inactivation of p53 by HPV E6 in these metastatic lesions appears to increase VEGF, angiogenesis and drive tumor progression making this a viable therapeutic target.[63]

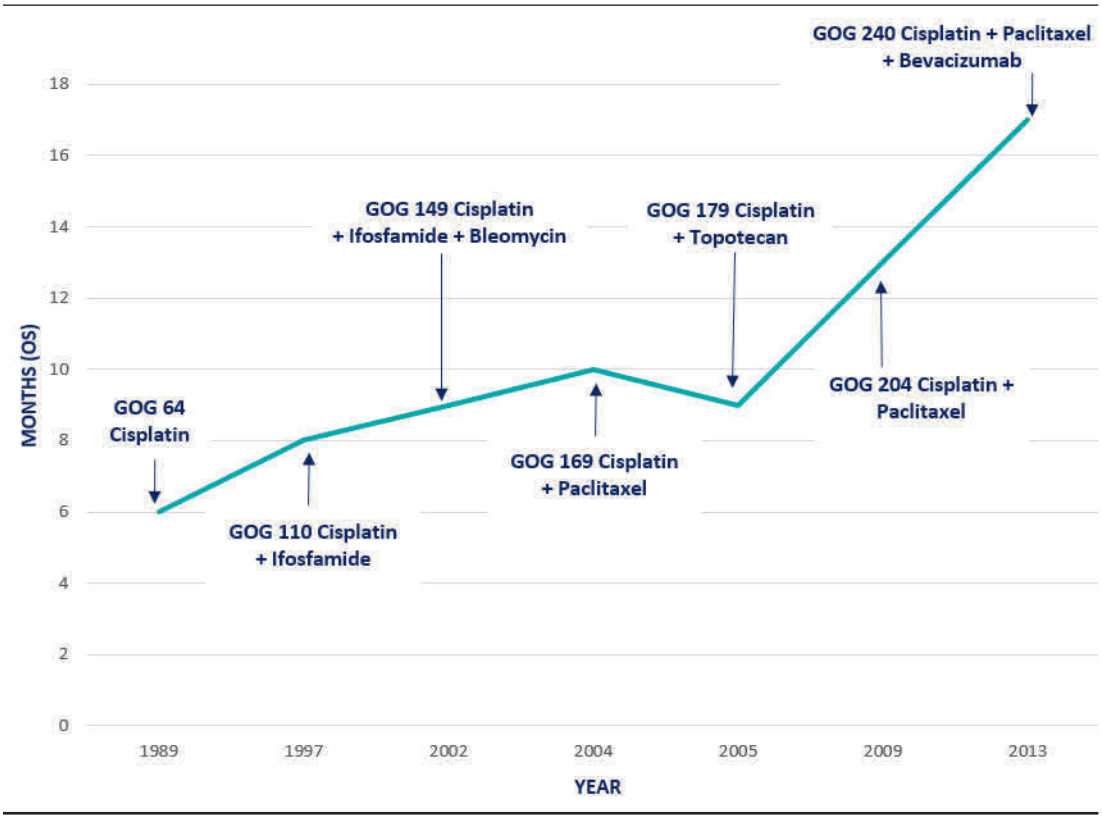
In 2009, the GOG launched protocol 240 to prospectively investigate the role of anti-angiogenesis therapy in treating metastatic and recurrent cervical cancer. In addition, the non-platinum doublet of paclitaxel plus topotecan was compared to the PC winner of GOG 204 since retreatment with cisplatin is less effective after primary concurrent radiation and chemotherapy (Table 7).

In spite of these adverse reactions (bevacizumab was associated with more grade 3-4 bleeding (5 vs 1%) thrombosis/embolism (9 vs 2%), and GI fistula (3 vs 0%)), in combination with the efficacy endpoint, changed the global standard of care.

Practice Changing Trials In Recurrent Cervical Cancer Second Line), also evolved the standard of care and led to the first FDA targeted approval in Gynecological Cancers, specifically cervical.

Although GOG 240 did not show an improvement associated with paclitaxel plus topotecan, it met its other primary endpoint of improving OS with the addition of bevacizumab. The bevacizumab-to-no- bevacizumab hazard ratio of death was 0.71 (97.6% CI 0.54-0.95; 1-sided p=0.0035). Median OS was 17 months (chemotherapy plus bevacizumab) and 13.3 months (chemotherapy alone). The RRs were 48% (chemotherapy plus bevacizumab) and 36% (chemotherapy alone) (p=0.0078). Treatment with bevacizumab was associated with more grade 3-4 bleeding (5 vs 1%) thrombosis/embolism (9 vs 2%), and GI fistula (3 vs 0%), but this additional toxicity did not adversely impact patient-reported score on the Functional Assessment of Cancer Therapy-Cervix Trial Outcome Index (FACT-Cx TOI).[67] This remarkable result again changed the global standard (Table 8), and the final overall survival data confirmed the benefit of bevacizumab, noting that the combination of chemotherapy with bevacizumab had a median OS of 16.8 months ver-

Table 8a. Treatment of Stage 4B, persistent and recurrent cervical cancer (First Line)



In spite of these adverse reactions (bevacizumab was associated with more grade 3-4 bleeding (5 vs 1%) thrombosis/embolism (9 vs 2%), and GI fistula (3 vs 0%)), in combination with the efficacy endpoint, changed the global standard of care.

sus 13.3 months for chemotherapy alone (HR 0.77, 95% CI 0.62-0.95, p=0.007).[68]

Incorporation of practice-changing Immunotherapy

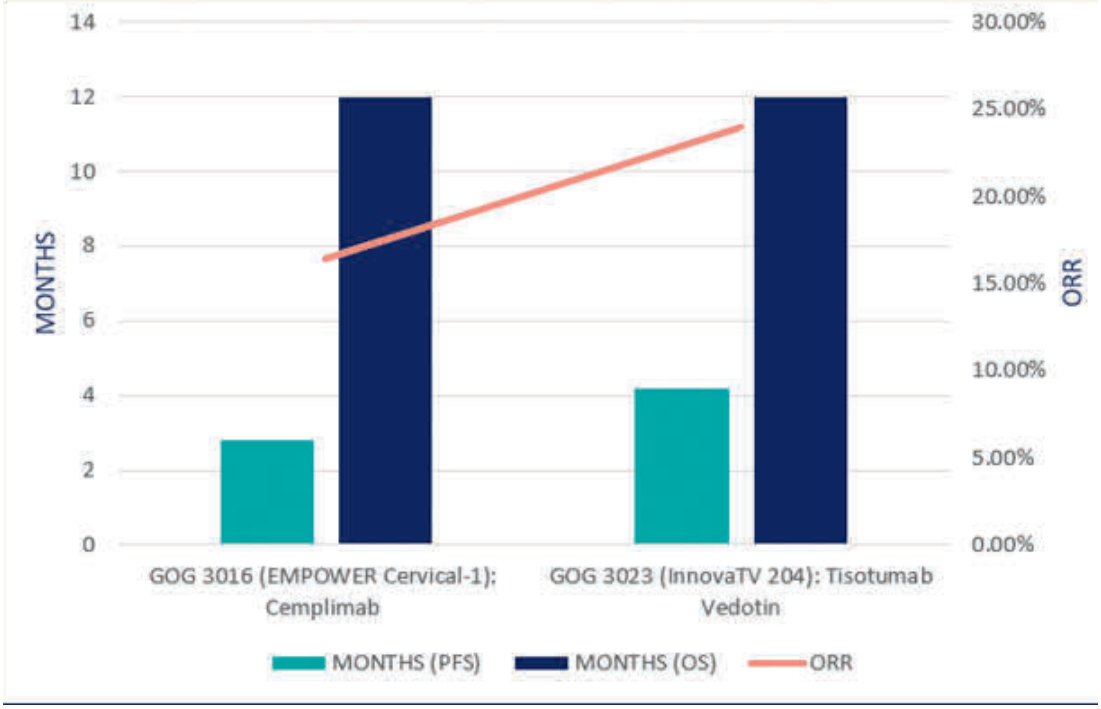
As GOG 240 ushered in the era of biologic therapy for cervical cancer, immunotherapy, specifically immune checkpoint inhibitors, were changing treatment paradigms in nearly all other solid tumor types. The virally mediated mechanism of carcinogenesis and antigenic immunogenicity generated enthusiasm to apply emerging immunotherapies to cervical cancer treatment.[69] Rapid development in this area during the integration of GOG into NRG Oncology resulted in some development occurring outside the GOG, but this work was essential to inform future group trials which would be done in direct partnership with industry and our global collaborators, especially ENGOT. These collective efforts, shown in the timeline in Table 9, resulted in rapid shifts in the treatment landscape, incorporating immunotherapy in nearly every treatment setting.

Early Experience

Enthusiasm for immunotherapy was fueled by early wins in the post-GOG 240 space. A most impactful proof of concept study was an NIH trial testing adoptive T-cell therapy (ACT) in the form of a single infusion of tumor-infiltrating T cells selected for HPV E6 and E7 reactivity (HPV-TILs).[70] The objective response rate (ORR) was 33% (3/9 patients), most notably 2 complete responses (CRs) that remained ongoing at 22 and 15 months, which was clearly unprecedented in this setting. This approach, however, was impractical due to the need for surgical biopsy of difficult to access tumors and pre-infusion lymphocyte-depleting chemotherapy followed by aldesleukin with risk of cytokine release syndrome. At this time, GOG 265 was designed as a two-stage phase 2 trial of axalimogene filolisbac (ADXS-HPV), an alternative approach utilizing Listeria monocytogenes as a vector to deliver anti-HPV-16 E7 antigen-adjuvant fusion protein to antigen presenting cells, which in turn activate HPV-specific effector T-cells.[71] This study met its primary endpoint of 12-month OS of 35% to warrant further study, supporting activation of GOG 3009/AIM2CERV within GOG Partners.

Single-agent checkpoint inhibitors offered a more straightforward approach and nivolumab was the first agent tested in NRG GY002, a single-arm, two-stage phase II study, also in the post-GOG 240 space.[72] In 25 evaluable patients, only one confirmed partial response (PR) (4%; 90% CI, 0.4%-22.9%) with a short duration of response (DOR) of 3.8 months was noted. Though 36% had stable disease (SD) (9/25; 90% CI, 20.2%-54.4%); the median duration of SD was still only 5.7 months (range, 3.5-12.7). PD-L1 expression (≥1%) was identified in 77.3% of tumors and did not appear to be predictive of response due to low ORR. This tempered enthusiasm for single anti-PD(L)1 therapy within the group, but concurrent trials combining anti-CTLA4 and anti-PDL1 strategies that

Table 8b. Practice Changing Trials In Recurrent Cervical Cancer (Second Line)



Practice Changing Trials In Recurrent Cervical Cancer Second Line), also evolved the standard of care and led to the first FDA targeted approval in Gynecological Cancers, specifically cervical.

were ongoing or late in development continued. GOG 9929 was a phase 1, locally advanced trial that enrolled and treated 32 eligible women with clinical Stage IB2 – IVA (FIGO 2009) with positive nodes on imaging to receive up to four doses of ipilimumab, a CTLA-4 inhibitor, at either 3mg/kg or 10mg/kg.[73] Of the 21 women that received ipilimumab, 10mg/kg every three weeks for four doses was the maximum tolerated dose. The median follow-up for patients was 14.8 months and was associated with a 12-month PFS rate of 81% and a 12-month OS rate of 90%. Building on this experience of the apparent safe administration of an immunotherapeutic agent following chemoradiation in GOG 9929, NRG-GY017 was designed to evaluate the role of the addition of three cycles of atezolizumab an anti-PD-L1 monoclonal antibody to chemoradiation for node positive locally advanced cervical cancer patients (ClinicalTrials.gov Identifier: NCT03738228). Atezolizumab was administered either as an immune primer three weeks prior to commencement of chemoradiation and/or in combination with chemoradiation for a total of three cycles in the two treatment approaches. On the study, 30 patients were evaluable for DLTs: none of the 16 patients on Treatment Arm A exhibited DLTs and three of the 14 patients on Treatment Arm B reported to have a DLT (8%). Overall, three patients on Arm Treatment A and 10 patients on Treatment Arm B experienced a grade 3 or higher treatment-related adverse event with only one being immune related. There was an increase in peripheral blood T-cell receptor (TCR) clonal expansion and expansion of tumor-associated T-cell clones between the start of treatment and day 21 of CRT in Arm A (p=0.0001) and Arm B (p=0.001). Patients with higher pre-treatment TCR diversity had increased likelihood of complete pathologic response in on-treatment biopsy (p= 0.049).[74]

Pivotal Immunotherapy Trials

Outside the group, KEYNOTE-158, a large basket trial of single agent, flat dose (200 mg IV q3 week) pembrolizumab for recurrent, metastatic cervical cancer enrolled 98 patients. By not following the traditional two-stage design, KEYNOTE-158 was able to detect clinically relevant activity that was isolated to 12 patients with PD-L1-positive tumors, for an ORR of 14.6% (95% CI, 7.8% to 24.2%. More importantly, these responses had long-term durability, with the median DOR not being reached (range, ≥ 3.7 to ≥ 18.6 months)[75] in the PDL1+ cohort. This activity, specifically its durability of response, secured accelerated approval for pembrolizumab in the second line or greater in the US. It also supported the incorporation of pembrolizumab and other immune checkpoint inhibitors into additional treatment settings and in combinations.

As these promising data emerged, the GOG and ENGOT were partnering with industry to conduct a randomized evaluation of PD1-inhibitor, cemiplimab, in patients who had disease progression after first-line platinum-containing chemotherapy, regardless of their PD-L1 status. In this study, EMPOWER-cervix/GOG 3016/ENGOT cx9, patients were randomized to cemiplimab (350 mg every three weeks) or the investigator's choice of single-agent chemotherapy.[76] In the 608 women were enrolled, cemiplimab was associated with a median OS advantage of

Table 9. The development of immunotherapy in cervical cancer

GOG trials

2018 NRG-GY002 2L+ nivolumab. Santin AD, et al. Gynecol Oncol. 2020 Apr;157(1):161-166.
2020 GOG 9929 CRT + ipilimumab. Mayadev JS, et al. JAMA Oncol 2020 Jan 6(1), 92-99
2021 EMPOWER-cervix/GOG 3016/ENGOT cx9. Tewari KS, et al. N Engl J Med. 2022 Feb 10;386(6):544-555.
2022 NRG GY017 atezolizumab + CRT. Mayadev J, et al. Paper presented at the Annual Meeting on Women's Cancer for the Society of Gynecologic Oncology. Phoenix, AZ

non-GOG trials

2015 HPV-TILs. Stevanović S, et al. J Clin Oncol. 2015 May 10;33(14):1543-50.)
2018 KEYNOTE 158. Chung HC, et al. J Clin Oncol. 2019 Jun 10;37(17):1470-1478.
2021 KEYNOTE 826. Colombo N, et al. N Engl J Med. 2021 Nov 11;385(20):1856-1867.
2022 CALLA. Monk B, et al. Intl Journ of Gyn Cancer. 2022;32: A2-A3.

12.0 vs. 8.5 months with a HR of 0.69; (95% CI] 0.56 to 0.84; two-sided p<0.001). Though the trial was enriched with squamous cell histology in response to emerging PDL1-specific benefit, OS benefit was found in both histologic subgroups (squamous-cell carcinoma and adenocarcinoma [including adenosquamous carcinoma]). Additional positive endpoints included PFS (HR 0.75; 95% CI, 0.63 to 0.89; two-sided P<0.001), ORR 16.4% vs 6.3% for cemiplimab and chemotherapy, respectively, and improvement in patient-reported quality of life measures including clinically meaningful measures of role functioning, appetite loss, and pain.[77] Though pembrolizumab was already available in the US, cemiplimab filled an important unmet medical need in Canada, Europe, Japan, and Brazil thus far.

Moving Immunotherapy to Earlier Lines of Treatment

Firstline systemic therapy for recurrent and metastatic disease

Building on the success of the GOG 240 regimen, the next logical setting to incorporate immune checkpoint inhibition was initial systemic therapy. To this end, the GOG Partners joined the Grupo Español de Investigación en Cáncer de Ovario (GEICO), ENGOT, JGOG and the GCIG to conduct a GOG 240 replacement, GOG 3030/BEATcc: Bevacizumab and Atezolizumab in Cervical Cancer.[78] BEATcc enrolled 404 patients with any PDL1 status who were randomized to the GOG 240 triplet with or without PDL1 inhibitor, atezolizumab, and treated to progression or toxicity. The primary endpoint at study inception was OS, but as effective second-line immunotherapy became more available for cross-over, PFS was added as a co-primary endpoint. As of this publication, enrollment has completed and sufficient PFS events accumulated to trigger the first interim analysis. There were no safety signals during the conduct of the trial.

As BEATcc accrued, an industry-sponsored trial conducted outside the cooperative groups, KEYNOTE-826, studied the addition of pembrolizumab in the same setting. This phase 3, randomized trial of the GOG 240 regimen (bevacizumab optional per physician choice) with or without pembrolizumab for 2 years duration, enrolled 617 patients, 89% whose tumors were PDL1+ and 64% of whom received bevacizumab. PFS and OS were both improved with the addition of pembrolizumab in both intention-to-treat (PFS HR 0.65; 95% CI, 0.53 to 0.79; P<0.001 and OS HR 0.67; 95% CI, 0.54 to 0.84; P<0.001)

and the PDL1+ (CPS 1) populations (PFS HR 0.62; 95% CI, 0.50 to 0.77; P<0.001 and OS 0.64; 95% CI, 0.50 to 0.81; P<0.001). The most common grade 3 to 5 adverse events were anemia (30.3% in the pembrolizumab group and 26.9% in the placebo group) and neutropenia (12.4% and 9.7%, respectively) with no detriment to quality of life. Moreover, 122 (42%) of 290 patients in the pembrolizumab group versus 85 (29%) of 297 in the placebo group had improved GHS–QoL at any time during the study (p=0·0003), consistent with EMPOWER-cervix findings and further underscoring the positive clinical impact of immunotherapy for these patients.[79]

Table 10. Response rates (and 95% confidence intervals (CI) where applicable) of immune checkpoint inhibitor combinations performed outside the NRG/GOG.

	n	ORR (95% CI)	ORR PDL1+	ORR PDL1-
Balstilimab +Zalifrelimab[1]	155	25.6% (18.8-33.9)	32.80%	9.10%
Cadonilimab[2]	100	33.0% (23.9-43.1)	43.80%	
Nivolumab 3 mg/kg + ipilimumab 1 mg/kg[3]	27	26% (11-46)	38%	8%
Nivolumab 1 + ipilimumab 3[3]	43	35% (21-51)	30%	29%

Incorporation into CRT Regimen for Locally Advanced Disease

The success of immunotherapy in later lines of treatment coupled with favorable phase 1 results reported in GOG 9929 and NRG GY017, plus a significantly improved OS with the addition of durvalumab maintenance following CRT for locally advanced non-small cell lung cancer provided rationale for incorporation of checkpoint inhibitors to CRT for locally advanced cervical cancer.[80] The first study to complete did so outside the GOG. CALLA randomized patients with FIGO 2018 IIIC1r-IVA 1:1 to durvalumab or placebo in combination with and following CRT for up to 24 months. With 770 patients randomized, durvalumab had comparable safety to standard CRT, but it unexpectedly did not significantly improve PFS.[81] Within the GOG, the KEYNOTE A18/GOG 3047/ENGOT cx11 study neared completion as CALLA resulted. This trial differs from CALLA in that it employs a PD1 inhibitor vs a PDL1 inhibitor and enrolled a slightly higher risk population with more nodal involvement than required for CALLA. The highly anticipated results are expected in 2023.

Looking Beyond Single-Agent Checkpoint Inhibitors

While the results of EMPOWER-cervix/GOG 3016/ENGOT cx9 and KEYNOTE 826 have been paradigm-shifting, survival advantages are driven by patients whose tumors respond to therapy. For anti-PD(L)1 treatments, these responses are mostly limited to PDL1+ tumors. Thus, increasing the number of responses to immune checkpoint inhibition would further improve outcomes. Dual checkpoint inhibition, with anti-CTLA4 and anti-PD1 combinations, demonstrates higher response rates over anti-PD(L)1 alone and doing so for both PDL1+ and PDL1- tumors (Table 10). This creates an opportunity for more patients to experience the durable benefit seen in those whose tumors respond. Table 10 summarizes the combinations or bispecifics that have been studied outside the NRG/GOG and led to ongoing and developing GOG trials.

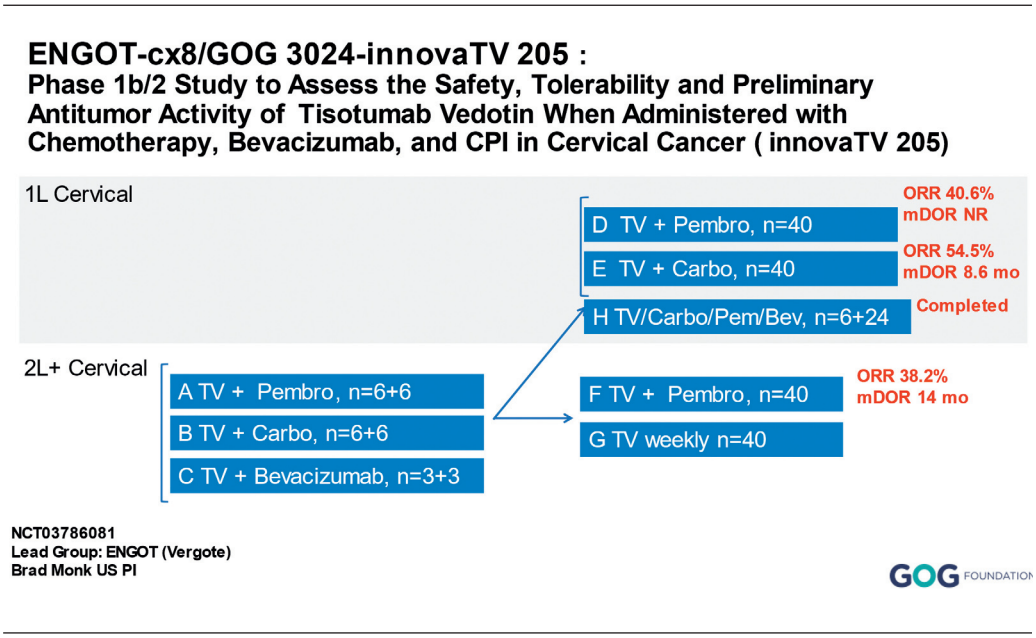
GOG Partners is conducting two current combination studies. GOG 3028/RaPiDS is a prospective, non-comparative trial of single agent anti-PD1 balstilimab and combination balstilimab/anti-CTLA4 zalifrelimab.[82] Efficacy assessed by ORR is the primary endpoint in each arm, and the non-comparative design will allow determination of the relative contribution of the CTLA4 component of the combination. Accrual has been completed and these results are also awaited in 2023.

Development of The First Antibody-drug Conjugate for Gynecologic Cancers, tisotumab vedotin

As immunotherapy moved into earlier lines of therapy, and for PDL1- patients, there remained an unmet medical need in the second line and beyond. Tisotumab vedotin (TV) is an antibody-drug conjugate (ADC) that targets cell surface tissue factor (TF) which is overexpressed in the majority of cervical cancers.[83] The drug is comprised of a monoclonal immunoglobulin G1 (IgG1) antibody against TF (HuMax-TF) conjugated to the microtubule-disrupting agent, monomethyl auristatin E (MMAE) using a protease-cleavable linker with an average of four molecules of vc-

MMAE per antibody. MMAE is delivered to TF-expressing cells to induce direct cytotoxicity and bystander killing of neighboring cells. In vitro studies have supported additional mechanisms of action through antibody-dependent cellular cytotoxicity, phagocytosis, and immunogenic cell death in in vitro studies.[84,85] A 27-patient phase Ib/2 trial of single-agent TV conducted outside the GOG established 2.0 mg/kg as the maximum tolerated dose and showed preliminary activity in a heavily pre-treated population (51% 2 prior lines of therapy) with an ORR of 22% (95% CI 12-35%) and median DOR of 6 months. The most common grade 3/4 treatment-emergent adverse events (AEs) were anemia (11%), fatigue (9%), and vomiting (7%).

Table 11.



With these promising results, a global phase 2 was activated under the ENGOT-GOG type C mechanism: innovaTV 204/ENGOT cx6/GOG 3023. This study enrolled 101 patients and reported at a median follow-up of 10 months. The confirmed ORR was 24% (95% CI 16-33%), with 7% complete responses and 17% partial responses, and a median DOR of 8.3 months—all of which outperformed the benchmarks of available chemotherapies in this space. The most common treatment-related adverse events included alopecia (38%), epistaxis (30%), nausea (27%), conjunctivitis (26%), fatigue (26%), and dry eye (23%). Grade 3 or worse treatment-related adverse events included neutropenia (3%), fatigue (2%), ulcerative keratitis (2%), and peripheral neuropathies (2% each with sensory, motor, sensorimotor, and neuropathy peripheral). A mitigation strategy for ocular toxicities developed during the conduct of the trial which included monitoring of visual acuity and corneal integrity, administration of preventative vasoconstrictive and corticosteroid eye drops, and cooling packs applied to the eyes before, during and after the 30 minute infusion.[86] innovaTV 204/ENGOT cx6/GOG 3023 supported an accelerated FDA approval for TV for in recurrent, metastatic cervical cancer in the second line or greater in September 2021. The confirmatory phase 3 trial, innovaTV301/ENGOT cx12/GOG 3057, randomizing patients to TV versus physicians' choice chemotherapy was already underway and closed in the US when TV became commercially available. It continued globally and completed enrollment in early 2023.

TV Combinations

The activity and tolerability of TV inspired combining the agent with other active cervical cancer agents. innovaTV205/ENGOT cx8/GOG 3024 was designed as an initial dose escalation of three combinations: TV + carboplatin, TV + pembrolizumab, and TV + bevacizumab in the second line or greater. The TV + bevacizumab combination carried particular concern for excess bleeding due to the TF target of TV and the known AE profile of bevacizumab. In this phase of the trial, each drug could be delivered at its standard dose in each combination, all q3 week schedules: TV 2.0 mg/kg, carboplatin AUC 5, pembrolizumab 200 mg, and even bevacizumab 15 mg/kg.[87] These 3 well-tolerated combinations were not only further studied for efficacy in the same treatment setting, but TV + carboplatin and TV + pembrolizumab were also studied in the frontline, GOG 240/KEYNOTE 826 space. The design of the phase 2 portion of innovaTV205/ENGOT cx8/GOG 3024 is shown in Table 11 along with the response rates demonstrated in the respective settings that have been reported to date. These results generated enthusiasm to add an Arm H to the design that investigates the replacement of paclitaxel in the GOG 240/KEYNOTE 826 regimen with TV, since they have similar mechanism of action, but TV has better tolerability--especially in regard to alopecia.

Future Directions

As is evidenced by this and other chapters, the influence

of the GOG Foundation in practice changing trials has shifted to being a key collaborator with NCI, industry, and our global partners in order to move the science forward faster and further. For cervical cancer, specifically, the goals of the next 50 years are to continue to reduce the burdens of disease and treatment by developing more effective and better tolerated therapies. The success of immunotherapy brings great promise, and optimization of the approach and timing, in addition to developing alternative targeted agents for those whose cancer progresses on immunotherapy, are the next frontier. Alternative targets include her2, PIK3CA, ARID1A, and PARP.[88,89] Secondary to preclinical work, the PARP inhibitor veliparib was combined with paclitaxel and cisplatin in a standard 3+3 phase dose escalation trial, GOG-76HH. Of the 34 women treated on protocol, the majority of which had recurrent squamous cell carcinoma diagnosed after chemoradiation, the dose level of 400mg twice daily in combination with chemotherapy was well tolerated and no maximal tolerated dose was identified. Overall, the median PFS was 6.2 months (95% CI 2.9 -10.1) and median OS was 14.5 (95% CI 8.2 – 19.4) suggesting another option to be evaluated in the management of advanced or recurrent cervical cancer.[90]

The increasing success of radical surgery, radiation and systemic therapy creates a need to better develop robust survivorship as women with cervical cancer are being cured more often and living longer. Accordingly, the GOG Cervical Cancer Committee has launched its first survivorship clinical trial (Clin- icalTrials.gov Identifier: NCT01649089). GOG 278 is a prospective evaluation of quality-of-life in patients undergoing non-radical surgery for early-stage cervical cancer (< 2cm) to determine the intermediate-term and long- term effects of surgery. Patients may undergo cold knife conization or a simple extrafascial hysterectomy as well as a pelvic lymphadenectomy. Like GOG 278 and ROCC, trials to improve not only longevity but also quality of life and cancer care experience are of great present and future interest.

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