Background (and Preamble):

Although cytologic screening programs with or without high risk human papillomavirus (HPV) DNA testing have dramatically reduced the incidence and mortality rates due to cervical cancer in developed countries, in the United States there are still over 12,000 new cases and 4,000 deaths attributable to this disease every year. Globally, cervical cancer is the third most common cause of cancer-related mortality in women with over 500,000 new cases and 250,000 deaths annually. Upon successful implementation, cervical cancer vaccination programs are expected to reduce the disease burden further.

Microinvasive and small tumor diameter cases (eg., International Federation of Gynecology and Obstetrics (FIGO) stages IA1-IB1 ≤2 cm) may be treated successfully with conization or radical trachelectomy plus lymphadenectomy in order to preserve the uterus for future childbearing if desired. Most early stage lesions (eg., FIGO IB2), however, are curable with radical hysterectomy, bilateral lymphadenectomy plus/minus tailed adjuvant therapy. Locally advanced cancers (FIGO stages IB2-IVA) are treated with cisplatin-based chemoradiation plus high-dose rate brachytherapy, but the recurrence rate approaches 50% which is unacceptable. To address this, adjuvant chemotherapy in this setting is being studied in the OUTBACK trial. Patients with isolated, central pelvic recurrences with no evidence of metastases may be salvaged through exenterative procedures. However, following the widespread adoption of chemoradiation protocols in which chemotherapy has been integrated for its use as a radiosensitizer and ability to eradicate subclinical micrometastases, most women who relapse following chemoradiation plus brachytherapy fail locally and at distant sites, precluding their candidacy for pelvic exenteration. Historically, the clinical course for women with unresectable persistent and recurrent disease, as well as those who present initially with metastatic cervical cancer (i.e, FIGO stage IVB), has been devastating, with systemic, platinum-based combination chemotherapy being typically palliative and associated with short-lived responses (or lack of response altogether due to acquired drug resistance from platinum exposure in the frontline setting with radiotherapy). In point of fact, GOG protocol 204 led by Monk et al\(^1\) was closed for futility at interim analysis when it was determined that none of the investigational platinum combinations (ie., topotecan, gemcitabine, vinorelbine) were expected to outperform the control, cisplatin-paclitaxel. Women with recurrent disease suffer from necrotic tumor in the irradiated field with concomitant tumor-related pain, neuropathy, renal failure and malnutrition, each of which individually or in combination may be associated with rapid deterioration of quality of life (QoL). Median survival is counted in months, with most of these relatively young women dying within seven to 12 months, leaving small children behind.
Clearly, the treatment of recurrent/metastatic cervical cancer has represented a high, unmet clinical need, and despite 8 phase 3 randomized clinical trials in this population conducted by the GOG, very little progress (if any) was made over three decades. Recognizing that the palliative platinum-paclitaxel chemotherapy doublet was demonstrating less activity among women who had received prior platinum with radiotherapy, the mandate sent to the GOG in 2006 by the National Cancer Institute’s (NCI) Cancer Therapy Evaluation Program (CTEP) was to explore the efficacy and tolerability of a non-platinum chemotherapy doublet in the 9th phase 3 randomized trial. Based on laboratory data by Bahadori et al suggesting synergy between topotecan and microtubule-modulating agents such as paclitaxel, and a phase II trial by Tiersten et al demonstrating the tolerability and reasonable activity of topotecan plus paclitaxel in preirradiated recurrent cervical cancer patients, the topotecan-paclitaxel chemotherapy doublet was selected as the investigational arm for what would ultimately become GOG protocol 240. However, many members of the GOG’s Cervical and Vulvar Medicine (CVM) Committee (chaired in 2006 by David H. Moore) remained concerned that “platinum resistance” in this disease was just a surrogate for “chemotherapy resistance”. A new approach to bring innovative interventions to patients with cervical cancer was needed.

Anti-Angiogenesis Therapy

In the initial developmental stages of GOG 240 in 2006, the fully humanized monoclonal antibody, bevacizumab, had received US FDA approval for treatment of non-small cell non-squamous lung cancer. In 2004 regulatory approval had been granted for the use of bevacizumab in colorectal cancer. Activity had been reported in breast cancer and the GOG was studying the incorporation of bevacizumab with chemotherapy in newly diagnosed ovarian cancer in GOG protocol 218. The mechanism of action through which bevacizumab is believed to exert its anti-angiogenic effect is through sequestration of the ligand, vascular endothelial growth factor (VEGF) so that it cannot bind the VEGF receptor (VEGFR), and thereby prevent the intracellular signal transduction cascade which leads to neovascularization to support continued tumor growth and metastasis.

**Figure 1. The process of tumor angiogenesis. (From the Public Domain)**

In response to a mass solicitation by CTEP, it was CVM Committee member Bradley J Monk who first suggested studying bevacizumab in cervical cancer. As the PI on the phase II trial, GOG protocol 227C, Monk studied bevacizumab monotherapy in heavily pretreated, previously irradiated women with recurrent cervical cancer and of over 20 agents studied in this series by the GOG, bevacizumab was the only one to meet predefined efficacy and safety thresholds to progress to the second stage of enrollment. Importantly, Monk enrolled several women at his (then) home institution of the University of California, Irvine and could see
patients responding. Together he and GOG Group Chair, Philip J DiSaia, MD along with members from the GOG senior leadership, Larry J. Copeland, MD and William T Creasman, MD worked with the GOG’s Protocol Development Committee (PDC) to build consensus to study anti-angiogenesis therapy in advanced (ie., persistent/recurrent/metastatic) cervical cancer.

Once approval from the PDC and Genentech, Inc had been granted, it was left to Study Chair and Principal Investigator (PI) Krishnansu S Tewari, MD to champion the trial before the Cervical Cancer Task Force, the Gynecologic Cancer Steering Committee, the Central Institutional Review Board, and CTEP. In these tasks he received immeasurable support from Monk, Harry J. Long III, MD (PI of GOG 1796 who suggested using a 2 x 2 factorial design to study both the non-platinum chemotherapy doublet topotecan-paclitaxel and bevacizumab in the same phase 3 trial) and Mike W. Sill, PhD the biostatistician who developed the robust (if not exceedingly complex) statistical design of GOG protocol 240.

Ultimately, permission to move forward was obtained following presentation of a fully developed rationale to study VEGF inhibition in this disease:

A. **Clinical rationale:** It has long been recognized that women with abnormal Papanicolaou testing who undergo colposcopic-directed biopsies will often have high grade dysplasia or even microinvasive carcinoma diagnosed in areas of abnormal vascular markings (eg., punctuation, mosaicism, atypical vessels). These areas represent harbors of angiogenesis and suggest that angiogenesis is important early in the pathogenesis of cervical cancer.

B. **Pathologic rationale:** In women with stage IB cervical carcinoma, Obermair et al demonstrated that high intratumoral microvessel density (ie, >20/field vs < 20 /field) was associated with worse 5-year survival (89.7% vs 63.0%). Thus, angiogenesis is a prognostic biomarker for frankly invasive disease. Microvessel density can be determined by light microscopy at 200x magnification and an examination are of 0.25 mm2 or through immunohistochemical staining for the endothelial cell antigen, CD31, found to line newly formed blood vessels.

C. **Therapeutic rationale:** the first evidence of the therapeutic efficacy of anti-angiogenesis therapy in cervical cancer was found in a phase I trial studying an angio-inhibitory protein TNP-470 synthetically derived from the antibiotic fumagillin which is secreted by the fungus *Aspergillus fumigatus fresenius*. Fumagillin was shown to inhibit endothelial cell proliferation and tumor-induced neovascularization but due to severe side effects, synthetic analogues were developed. In the phase I trial of 18 women with recurrent and metastatic cervical cancer, one patients experienced a complete response with resolution of numerous pulmonary metastases and was published separately as a case report in the New England Journal of Medicine. This was followed by demonstrable anti-angiogenesis activity of single agent bevacizumab in a phase II trial studying heavily pretreated women with advanced cervical cancer (GOG 227C, discussed earlier), and the superiority of anti-VEGF therapy (pazopanib) over anti-EGF therapy (lapatinib) in a randomized phase II trial by Monk et al in a similar population of women with recurrent disease.
D. **Molecular rationale:** High risk subtypes of the human papillomavirus (HPV) in their native form exist as a double strand DNA virus that replicates as an episome and does not induce malignant transformation. This is due to the regulatory viral gene, E2, preventing transcription of the viral oncoproteins E6 and E7. It has been known for some time that viral integration into host DNA is required for transformation and the integration point lies in the E2 reading frame, thus relieving transcriptional repression of E6 and E7. The viral oncoproteins interact with cellular tumor suppressor gene products, with E6 ultimately degrading p53 and E7 inactivating pRetinoblastoma. This molecular cascade produces increased levels of thrombospondin-1 and hypoxia-inducible factor-alpha, both of which lead to VEGF production and tumor angiogenesis. Sequestration of VEGF with the fully humanized monoclonal antibody bevacizumab can block this process.

![Figure 2. A molecular rationale to study anti-VEGF therapy in cervical cancer.](image)

**The GOG 240 Steering Committee**

Joining Tewari, Sill, Long, and Monk were Helen E. Michael, MD (pathologist), co-chairs Richard T. Penson, MD (health-related QoL), David Moore (prognostic markers), Steven E. Waggoner, MD (impact of tobacco use), Michael J. Birrer, MD, PhD (circulating tumor cells (CTCs), and Julie Smith, RN from the NCI-Designated Chao Family Comprehensive Cancer Center at the University of California, Irvine (Tewari’s home institution). Robert A. Burger (PI of GOG 218 and affiliated with the Fox Chase Cancer Center in Philadelphia during GOG 240 protocol development), Mark F. Brady, PhD (director of statistics), and Frederick B. Stehman, MD (director of publications committee and member of the data safety monitoring board (DSMB)) provided active guidance during the conduct of GOG 240. Additional support by the GOG throughout pre-development and study conduct would come from John A. Blessing, PhD (executive director of the Statistical Data Center), Mark F. Brady, PhD (director of statistics), Laura L. Reese (executive director of operations), Kia Neff (director of clinical trials development), Meg Colahan (protocol administrator), Cathy Galoppo (information systems manager), Angela M. Kuras, BA (assoc director data management), Kim M Blaser (clinical trials editorial associate), and Anne M. Reardon (clinical trials editorial associate). Support from the
NCI was originally assigned to Edward L. Trimble, MD who brokered the deal to open GOG 240 at several cancer centers in Spain through GEICO (Spanish Group for Investigation on Ovarian Cancer), and was then passed on to Jo Anne Zujewski, MD and finally to Elise C. Kohn, MD. Two gynecologic oncologists at Genentech, Katherine Y. Look, MD and Amreen Husain, MD rounded out the GOG 240 steering committee to provide regulatory support should the trial meet one or both of its primary endpoints. It should be noted, however, that at the time of protocol development, following review by the US Food and Drug Administration, both Monk and Group Chair PJ DiSaia were required to ascertain that GOG 240 was not a registration trial.

**Trial Activation, Conduct, and Closure**

GOG protocol 240 was activated on April 9th, 2009. At that point, Monk had succeeded Moore as Chair of the CVM committee and following a 7-month period during which time investigators were getting the study approved through their local Institutional Review Boards, accrual began to steadily climb until January 2012 when the trial had met its accrual goal (n=452). In GOG 240, women with recurrent/persistent or metastatic cervical cancer were randomized to one of two chemotherapy backbones (cisplatin-paclitaxel (control) or topotecan-paclitaxel) with or without bevacizumab (15 mg/kg). Unique to GOG trials in this patient population, patients were treated every 21 days until progression (or unacceptable toxicity), and eligibility required normal renal function and a GOG performance status of 0 or 1. In previous trials it had not been unusual to have had relatively sick patients on study and the steering committee felt strongly that for the investigational arms to be able to demonstrate a significant reduction in the hazard of death by 30% (the primary endpoint was overall survival (OS)), then the study needed to be performed in the “healthiest” cohort of the recurrent/metastatic cervical cancer population. Therefore, medical comorbidities had to be optimized, malnutrition had to be corrected, and tumor-related and neuropathic pain had to be controlled prior to study entry. In hindsight, this “sanitization” of the eligibility criteria were seen as being critical to the success of the study.
Figure 3. GOG 240 schema.

In February 2012, 174 deaths had been entered which triggered the single interim analysis specified by the protocol. At that time, there was a signal that bevacizumab was active but given the recent decision to withdraw US FDA accelerated approval of bevacizumab in breast cancer, the decision made by the DSMB and the GOG 240 steering committee was to ascertain the strength of the signal in a subsequent data lock. The first interim analysis did however answer the question regarding the substitution of topotecan for paclitaxel in the non-platinum chemotherapy doublet. Specifically, the arms administering topotecan-paclitaxel (TP) were not superior to the control, cisplatin-paclitaxel (CP). Median survival for CP vs TP was 15 vs 12.5 mos, respectively (HR 1.20; 99% CI, 0.82-1.76; p=0.88). Because the trial had not been designed for non-inferiority, patients were permitted to remain on the non-platinum doublet (if tolerable) as the trial continued. At the request of Warner K. Huh, MD (Program Committee Chair for the 2013 Society of Gynecologic Oncology (SGO) Annual Meeting on Women’s Cancer), the data from the first interim analysis concerning non-superiority of topotecan-paclitaxel was presented as GOG 240.1 in the plenary session (Abstract #1). The paper won the SGO Presidential Award for the most outstanding scientific abstract and the Hugh RK Barber, MD Lectureship Designation. Unfortunately, despite a large amount of impactful data on the use of the non-platinum chemotherapy doublet in this population (particularly concerning toxicology), the session moderator at the SGO chose to focus his line of questioning only on bevacizumab despite being told numerous times that those data were not yet mature.

In December 2012 a second database snapshot was taken (at 271 deaths as specified by the DSMB following the first interim analysis) and following a careful analysis it was determined in January 2013 that the trial had met its primary endpoint. The Study Chair (Tewari) was in India teaching a robotic surgery course for gynecologic oncologists at Apollo Hospital in Kolkata and remembers very well being awake at 3 am (on the NCI’s schedule) assisting with the NCI Press Release during a conference call and then preparing the abstract the following night (also at 3 am) with Dr. Zujewski from the NCI. The drama that then ensued concerning which meeting to submit the abstract to (ie, to the SGO or to the American Society of Clinical Oncology (ASCO)) was overwhelming (for Tewari) and finally, following an intervention by 2013 SGO President Ronald D Alvarez, MD, the steering committee agreed to send it to ASCO since the SGO had received the abstract for GOG 240.1 The NCI’s February 2013 Press Release noting that bevacizumab increased survival in advanced cervical cancer coincided with ‘Dear Doctor’ and ‘Dear Patient’ Letters (drafted by Tewari and approved by the NCI) alerting all living patients and treating physicians of the trial results. Arrangements were made with the NCI and Genentech for provision of bevacizumab to patients alive on the topotecan-paclitaxel arms. The meeting was still four months away and ASCO made a rare exception to the embargo policy and released the abstract into the public domain in March 2013, three months before the GOG could get to the podium to present the data. The abstract (referred to as GOG 240.2) was still accepted into the General Plenary (abstract #3) and featured in the ASCO 2013 Press Briefing. (The General Plenary at ASCO is notable for its selection of the top 5 abstracts from out of over 5,500 abstracts submitted each year to the Annual Meeting.)
GOG 240 met its primary endpoint in that the arms administering bevacizumab were found to significantly increase overall survival (OS) by 3.7 months (17.0 vs 13.3 mos; HR 0.71; 98% CI, 0.54-0.95; p=0.004). Although this was significant at the 5% level, because of the alpha-spending function at interim, the confidence interval is reported at 98% instead of 95%. In addition to OS, there was a significant improvement in progression-free survival (PFS) (8.2 vs 5.9 mos; HR for progression, 0.67; 95% CI, 0.54-0.82; p=0.002) and response rate (RR) (48% vs 36%; relative probability of response, 1.35; 95% CI, 1.08-1.68; p=0.008), all without a significant deterioration in health-related quality of life (HRQoL) as measured by patient-reported outcomes using three previously validated QoL instruments (Functional Assessment of Cancer Therapy – Cervical Cancer Trial Outcome Index, the GOG Neurotoxicity subscale, and the Brief Pain Inventory). Important findings concerning toxicology included grade 2+ fistula in 8.6% of patients treated with bevacizumab. No new safety signals were reported, with both bevacizumab-induced grade 2+ hypertension (24%) and grade 3 venous thromboembolism (8%) occurring at or below predicted rates.

![Figure 4. Kaplan Meier curves for overall survival at the second interim analysis.](image)

The QoL data (GOG 240.3) were presented by Penson as a Late-Breaking Abstract several months later in Amsterdam, Netherlands at the 2013 Annual Meeting of the European Society of Medical Oncology (ESMO). This was followed by a poster presentation of cost-effectiveness of bevacizumab in advanced cervical cancer using GOG 240 data in a Markov Decision Tree (GOG 240.11) by L. Minion at the 2013 Biennial Meeting of the European Society of Gynaecological Oncology in Liverpool, UK.

Previously, former GOG CVM Committee Chair and PI of GOG 169, DH Moore had pooled clinical prognostic factors from previous phase 3 GOG trials in the advanced cervix population and in his model (widely referred to as the Moore criteria), five factors of equal weight were identified: performance status >0, African American race, short time to recurrence (< 12 mos), prior platinum exposure, and pelvic disease. Patients who were low-risk on the Moore scale (0-1 factor) experienced a significantly better (albeit short-lived) response to palliative systemic therapy than those who were mid-risk (2-3 factors) or those who were high-risk (4 or 5 factors). During the developmental phases of GOG 240, there were some members of the CVM committee who felt that patients denoted to be high-risk by the Moore criteria...
should not be permitted to enroll on GOG 240 and should be directed to a different trial or even to best supportive care/hospice. Wisely, Monk intervened and pointed out that the Moore criteria had been identified retrospectively and that they needed to be prospectively studied.

This then became a tertiary objective of GOG 240 (ie., GOG 240.4) and the prospective validation of the Moore criteria was presented by Tewari in plenary session at the SGO’s 2014 Annual Meeting on Women’s Cancer in Tampa, FL. Interestingly, high-risk patients derived the greatest benefit from bevacizumab (12.1 vs 6.3 mos OS; HR 0.536; 95% CI, 0.32-0.905; p=0.0196) while there did not appear to be a survival advantage for low-risk patients treated with bevacizumab (22.9 vs 21.8 mos; HR 0.96; 95% CI, 0.51-1.83; p=09087). Thus while high-risk patients (a group some wanted to exclude from trial participation) and mid-risk patients may accept the potential toxicity of anti-angiogenesis therapy, women that are low-risk may be counseled against it, particularly if they are at high risk for fistula (see discussion below). In any event, the Moore criteria represent the first prospectively validated scoring system in this disease and are easy to compile. It should be noted that because African Americans with cervical cancer have similar clinical outcomes to Caucasians when the playing fields are level (eg., studies from the military or from the Kaiser Permanente Health Maintenance Organization), in GOG 240, African American ethnicity may simply represent a surrogate for impaired/lack of access to healthcare, suggesting that the Moore criteria may be applicable even to populations in which African Americans do not comprise a significant percentage.

While the Moore criteria are now embraced by the NRG/GOG cognoscenti, the dissemination of the scoring system outside of the United States where most of the cervical cancer burden manifests is difficult to track.

During the first quarter of 2014, the protocol-specified 348th death was recorded and the final survival analysis (GOG 240.7) was undertaken and presented by Tewari as a Late-Breaking Abstract at ESMO in Madrid, Spain. In an intent-to-treat analysis (in which 20 women initially randomized and treated on the chemotherapy alone arms who went on to receive bevacizumab when the second interim analysis was reported), the survival curves remained separated at over 50 months of follow-up (16.8 vs 13.3 mos; HR 0.765; 95% CI, 0.62-0.95; p=0.0068).
Towards year’s end, two important approved GOG 240 ancillary data projects were presented in plenary session at the 2014 Biennial Meeting of the International Society of Gynecologic Cancer in Melbourne, Australia: risk factors for fistula (GOG 240.9) by L. J. Willmott, MD in the President’s Game Changer’s opening plenary, and impact of histology (GOG 240.8) by L. M. Seamon, DO. Willmott et al reported that all women who developed fistula on GOG 240 had been previously irradiated with additional risk factors including pre-existing hypertension, current tobacco use, and pelvic disease. Seamon et al performed a binary exchange analysis using pooled data from phase 3 advanced cervix studies that included patients with adenocarcinoma and adenosquamous histology (GOG 240, 204, and 179) and showed that OS between women with glandular lesions and squamous histology was not significantly different when treated with systemic therapy.

In 2015, one of the translational objectives of GOG 240 (i.e, GOG 240.5) was presented by Tewari in the plenary session of the SGO’s Annual Meeting on Women’s Cancer in Chicago, IL. GOG 240.5 was a proof-of-concept that circulating tumor cells (CTCs) could be found in the serum of women with advanced cervical cancer. In an exploratory analysis, among patients with high pre-treatment CTCs, treatment with bevacizumab reduced the hazard of death and progression (HR 0.57;95% CI, 0.32-1.03), (PFS HR 0.59;95% CI, 0.36-0.96). The prognostic impact of tobacco use in this population (GOG 240.6, Waggoner et al) and the approved ancillary data study on complete responders (GOG 240.10, Eskander et al) were also presented at the 2015 SGO Meeting in the poster session.

Publication Schedule

The primary analysis, GOG 240.2 (presented at the 2013 ASCO) was published in the New England Journal of Medicine on February 20, 2014. Included in the author string were appointed physicians from the sites with the highest accruals, including L. M. Ramondetta, MD from the MD Anderson Cancer Center in Houston, TX; L. M. Landrum, MD from the University of Oklahoma; A. Oaknin, MD from Vall d’Hebron University Hospital in Barcelona, Spain; T. J. Reid, MD from University of Cincinnati Women’s Cancer Center in Kettering, OH; and M. M. Leitao, MD from Memorial Sloan-Kettering Cancer Center in New York. The quality of life analysis (GOG 240.3), the prospective validation of the Moore criteria (GOG 240.4), and the cost-effectiveness study (GOG 240.11) appeared in 2015 in Lancet Oncology, Clinical Cancer Research, and Gynecologic Oncology, respectively.

At present, three manuscripts are under review with the NRG Oncology Publications Committee: GOG 240.5 (circulating tumor cells), GOG 240.7 (final protocol-specified survival analysis), and GOG 240.8 (histology). Manuscripts for both GOG 240.6 (smoking) and GOG 240.10 (complete responders) are being prepared. Unfortunately due to reasons unknown (but most likely a result of collateral damage from the cooperative group merger that dissolved the original GOG Ancillary Data committee and replaced it with the NRG Oncology Secondary Analysis committee), work on the GOG 240.9 manuscript (fistula) has reached an insurmountable impasse as the writing team has not been provided with the much needed QoL
scores and other pertinent data necessary for a complete analysis. This is disappointing because
the development of fistula is seen as a very important adverse event on GOG 240 and there is
an obligation to provide both treating oncologists and the public with as much information as
there is available on this complication as expeditiously as possible. It has nearly been two years
since GOG 240.9 was presented in the IGCS Game Changer’s plenary session. It should be noted
that there is an ongoing safety trial specifically evaluating gastrointestinal (GI) safety of
bevacizumab (as defined by the frequency and severity of GI perforation/fistula, GI-vaginal
fistula, and genito-urinary fistula) which may help address some of these questions in the
future (ClinicalTrials.gov identifier NCT02467907).

Global Impact of GOG 240
Within one week of publication of GOG 240.2 in the NEJM, the United Kingdom’s Cancer
Drug Fund announced that bevacizumab had been approved for women in England with
recurrent and metastatic cervical cancer. While Genentech had been “pleased” to support the
phase 3 trial it was not the company’s intent from design to file GOG 240. However, when
Genentech learned in Q1’2013 that the study’s OS endpoint had been met and that the NCI was
planning to issue a Clinical Alert indicating that the data were “practice-changing” and should
be made known to the general public, did Genentech elect to proceed with bringing data
inhouse to file. On July 14, 2014, Genentech issued a press release stating that the US FDA had
agreed on priority review of their application to expand the label of bevacizumab. On August
14, 2014, regulatory approval by the FDA was granted, making this the first targeted agent to
be granted FDA approval for any gynecologic cancer. Both triplet regimens studied in GOG 240
were approved by the FDA (cisplatin-paclitaxel-bevacizumab and topotecan-paclitaxel-
bevacizumab). Interestingly, having obtained several outstanding (ie., late submissions) data
forms from the time of the second interim analysis, the FDA package insert lists the median
improvement in OS as 3.9 months (as opposed to 3.7 mos reported at ASCO). Both triplets have
also been designated Category 1 by the National Comprehensive Cancer Network (NCCN)
Cervical Cancer Treatment Guidelines, indicating that due to overwhelming data and universal
NCCN consensus that the intervention is appropriate.

Swissmedic approved bevacizumab for cervical cancer on December 22, 2014, and
following a positive opinion issued on February 27, 2015 by the Committee for Medicinal
Products for Human Use, the European Medicines Agency approved bevacizumab for cervical
cancer for the entire European Union on April 8, 2015.

GOG 240 has also resulted in regulatory approval of bevacizumab for advanced cervical
cancer in Canada and Mexico, two Central American countries (Panama and Costa Rica),
Colombia, Argentina, Ecuador, Chile, Peru, and Brazil. Approval has also been granted in
Ireland, Australia, Morocco, South Africa, Israel, Lebanon, Turkey, four Gulf countries (Bahrain,
Oman, Kuwait, and Qatar), and the United Arab Emirates. Finally, bevacizumab has also now
been approved in several Asian countries, including, India, Hong Kong, Korea, Japan, Malaysia,
Singapore, and Vietnam.
It is astonishing that GOG 240 would have such a large impact worldwide. During the Q&A session following the General Plenary at ASCO in 2013, one of the issues the study team had been called out on was how we were planning to get such an expensive drug such as bevacizumab to the developing world where the incidence and mortality rates due to cervical cancer are highest? At that time Monk intervened and told the audience that GOG 240 was not designed for the developing world, rather it was carried out for developed nations. With that being said we conceded that while the impoverished nations need to divert resources to screening and vaccination (ie., prevention), we did feel an obligation to help those struggling with advanced disease today.

Unlike the situation in the United States, however, regulatory approval does not necessarily translate to the drug being provided for patients. Post-approval market research by Genentech suggests that there has been over 75% uptake of bevacizumab in the advanced cervix population in the U.S. Without government intervention in the poorer countries, poor women with advanced disease are not likely to be treated with bevacizumab. The situation is confounded further by the fact that in the developing world, many of the women with advanced cervical cancer are not as “healthy” as those studied in GOG 240. Other region-specific issues appear insurmountable. For example, in Brazil, the forest women from the Amazon have to journey 11 hours by boat to reach facilities where treatment for advanced cervical cancer is available. In South Africa, there is a large HIV+ subpopulation among the cervical cancer patients for whom adequate antiretroviral therapy is not available resulting in low CD4 counts which preclude treatment with chemotherapy plus bevacizumab. And in several areas of the world where the drug is readily available, oncologists have allowed their fear of fistula to essentially paralyze them from administering anti-angiogenesis therapy despite the near incurability of the disease afflicting their patients. However, creative government policies (eg., in Ecuador bevacizumab is approved for several indications but only provided by the government to patients with colorectal cancer and cervical cancer) and the advent of less costly biosimilars are likely to help get drugs like bevacizumab to patients in need the world over. For these reasons, the positive impact of GOG 240 that has manifested globally, especially in Latin America, regions of Africa, and in Asia, is viewed as an important contribution.

Although a median improvement in OS of 3.7-3.9 mos is not likely to cure women with advanced cervical cancer, in the eyes of the world, some progress has finally been made in this disease. For the first time we have a foot in the door and identified a potential therapeutic window of opportunity through which patients deriving benefit from bevacizumab may be treated with other novel agents prior to progression (eg., other classes of anti-angiogenesis therapy, immunotherapy including checkpoint inhibitors and vaccines)

It is a testament to both NRG Oncology and the NCI that this trial was conducted in a population of relatively young women addressing a high, unmet, clinical need. In the truest sense of the word, GOG 240 represents a robust collaboration among patients and their families, GOG investigators throughout the country (US/Canada/Spain), GOG support staff and senior leadership, the NCI, and Genentech, Inc. It was the GOG’s final phase III randomized trial in advanced cervical cancer, having completed accrual prior to the NCI-mandated cooperative
group merger from which NRG Oncology has emerged. As such, GOG 240 has a place on the shelf next to the important phase III randomized studies that preceded it, including GOG 204, 179, 169, 258, 249, 209, 122, 213, 212, 263, 252, 218, 182, 172, 154, 111, etc.

The GOG 240 study team expresses gratitude to steering committee members outside of the GOG, including our scientific colleagues from Genentech, Inc (Katherine A. Look, MD and Amreen Husain, MD) and to Elise C. Kohn, MD from the NCI to whom the task has fallen to keep the machinery running on all components of the trial since inheriting the burden following the 2013 ASCO Meeting.

The author (KST) would like to dedicate this article to the memory of one of his two mentors on GOG 240, Dr. Harry J. Long III, MD who made important contributions to the design of GOG 240 and was readily available for assistance with complex chemotherapy-related queries submitted to the PI during the approximate four years that the trial was open for accrual. Dr. Long tragically passed away in a car accident one month before it was determined that GOG 240 had demonstrated a survival advantage associated with the arms administering bevacizumab.

Special appreciation to NRG Oncology Group Chair, Philip J. DiSaia, MD for having given the PI many experiences over years, including the unique opportunity to participate in GOG 240. Tremendous gratitude to brothers-in-arms, Mike W. Sill, PhD and Richard T. Penson, MD, for their contributions to trial design and data interpretation, support of the PI (especially during ASCO), and continued friendship. Last but not least, to the mentor from whom the idea to study anti-angiogenesis therapy in cervical cancer originated, Bradley J. Monk, MD – thank you for an incredible journey these past 24 years!

This invited article was written by K.S. Tewari from an economy aisle seat on the Southwest Airlines flight 1189 returning to LAX from the Mini-Symposium on Immunotherapy in Cervical Cancer held on Wednesday August 10, 2016 in Building 22 at the United States Food and Drug Administration in Baltimore, MD.

(Those who have the time to read this sprawling narrative should read between the lines. There’s a lot going on…)

References:


