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Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240)

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Summary

Background On Aug 14, 2014, the US Food and Drug Administration approved the antiangiogenesis drug bevacizumab for women with advanced cervical cancer on the basis of improved overall survival (OS) after the second interim analysis (in 2012) of 271 deaths in the Gynecologic Oncology Group (GOG) 240 trial. In this study, we report the prespecified final analysis of the primary objectives, OS and adverse events.

Methods In this randomised, controlled, open-label, phase 3 trial, we recruited patients with metastatic, persistent, or recurrent cervical carcinoma from 81 centres in the USA, Canada, and Spain. Inclusion criteria included a GOG performance status score of 0 or 1; adequate renal, hepatic, and bone marrow function; adequately anticoagulated thromboembolism; a urine protein to creatinine ratio of less than 1; and measurable disease. Patients who had received chemotherapy for recurrence and those with non-healing wounds or active bleeding conditions were ineligible. We randomly allocated patients 1:1:1:1 (blocking used; block size of four) to intravenous chemotherapy of either cisplatin (50 mg/m² on day 1 or 2) plus paclitaxel (135 mg/m² or 175 mg/m² on day 1) or topotecan (0·75 mg/m² on days 1–3) plus paclitaxel (175 mg/m² on day 1) with or without intravenous bevacizumab (15 mg/kg on day 1) in 21 day cycles until disease progression, unacceptable toxic effects, voluntary withdrawal by the patient, or complete response. We stratified randomisation by GOG performance status (0 *vs* 1), previous radiosensitising platinum-based chemotherapy, and disease status (recurrent or persistent *vs* metastatic). We gave treatment open label. Primary outcomes were OS (analysed in the intention-to-treat population) and adverse events (analysed in all patients who received treatment and submitted adverse event information), assessed at the second interim and final analysis by the masked Data and Safety Monitoring Board. The cutoff for final analysis was 450 patients with 346 deaths. This trial is registered with ClinicalTrials.gov, number NCT00803062.

Findings Between April 6, 2009, and Jan 3, 2012, we enrolled 452 patients (225 [50%] in the two chemotherapy-alone groups and 227 [50%] in the two chemotherapy plus bevacizumab groups). By March 7, 2014, 348 deaths had occurred, meeting the prespecified cutoff for final analysis. The chemotherapy plus bevacizumab groups continued to show significant improvement in OS compared with the chemotherapy-alone groups: 16·8 months in the chemotherapy plus bevacizumab groups versus 13·3 months in the chemotherapy-alone groups (hazard ratio 0·77 [95% CI 0·62–0·95]; p=0·007). Final OS among patients not receiving previous pelvic radiotherapy was 24·5 months versus 16·8 months (0·64 [0·37–1·10]; p=0·11). Postprogression OS was not significantly different between the chemotherapy plus bevacizumab groups (8·4 months) and chemotherapy-alone groups (7·1 months; 0·83 [0·66–1·05]; p=0·06). Fistula (any grade) occurred in 32 (15%) of 220 patients in the chemotherapy plus bevacizumab groups (all previously irradiated) versus three (1%) of 220 in the chemotherapy-alone groups (all previously irradiated). Grade 3 fistula developed in 13 (6%) versus one (<1%). No fistulas resulted in surgical emergencies, sepsis, or death.

Interpretation The benefit conferred by incorporation of bevacizumab is sustained with extended follow-up as evidenced by the overall survival curves remaining separated. After progression while receiving bevacizumab, we did not observe a negative rebound effect (ie, shorter survival after bevacizumab is stopped than after chemotherapy alone is stopped). These findings represent proof-of-concept of the efficacy and tolerability of antiangiogenesis therapy in advanced cervical cancer.

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Introduction

With an estimated annual incidence of 529 800 new cases and 275 100 deaths globally in 2011, cervical cancer continues to represent a substantial cause of morbidity and mortality among predominantly young and middle-aged women (20–60 years) throughout the world.[1]

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Research in context

Evidence before this study

We searched PubMed for articles published in English between Jan 1, 1980, and March 31, 2017, with the search terms "recurrent", "metastatic", "cervical cancer", "treatment", "therapy", anti-angiogenesis", "phase I", "phase II", and "phase III". On the basis of the activity of the antiangiogenesis drug bevacizumab in colorectal cancer and other solid tumours, vascular endothelial growth factor (VEGF) emerged in the first decade of the 21st century as an important molecule to target to prevent tumour angiogenesis. After a second interim analysis of the phase 3 randomised controlled trial of chemotherapy with and without bevacizumab for women with recurrent, persistent, or metastatic cervical carcinoma, the National Cancer Institute reported in a press release that the study had met one of its primary endpoints in that addition of bevacizumab to two distinct chemotherapy doublets resulted in a significant overall survival advantage compared with patients receiving chemotherapy alone.

Added value of this study

Concerns remained about whether or not the overall survival difference from the second interim analysis was robust, clinically meaningful, and would persist in final analysis. This final prespecified analysis was done after 348 deaths and substantiates that the overall survival advantage observed at the interim analysis has been sustained, despite a number of women in the control chemotherapy groups crossing over to the bevacizumab groups after the National Cancer Institute press release. Importantly, response to bevacizumab was not associated with early death after progression as evidenced by the detailed postprogression survival analysis. Finally, longer follow-up than after the second interim analysis has provided greater precision in characterisation of the adverse event profile, allowing for accurate estimation of the occurrence of venous thromboembolism and permitting separation of gastrointestinal perforation events (a surgical emergency) from development of gastrointestinal-vaginal and genitourinary-vaginal fistula.

Implications of all the available evidence

Incorporation of bevacizumab in treatment of recurrent, persistent, or metastatic cervical cancer is practice changing, as evidenced by adoption and endorsement of this therapy by multiple regulatory agencies throughout the world. Cervical cancer remains a major health problem globally and, while screening and prevention (ie, vaccination) programmes need to be established in low-income countries, for the first time in decades, a small therapeutic window of opportunity has been identified in management of advanced cervical cancer through which patients deriving benefit from chemotherapy plus bevacizumab can be treated with other active novel agents before progression. Toxicity requires continued assessment, particularly in cases of fistula formation.

A clearer example in health care than cervical cancer is unlikely to be found in which the lines that separate high-income and middle-income societies from low-income societies are more readily discernible. For example, the annual incidence of cervical cancer in England was 2900 cases in 2010, with a mortality of 1000, whereas in the USA, the American Cancer Society estimates that only 12 820 new cases will occur in 2017, with 4210 deaths.[2] In Europe, cervical cancer is the sixth most common cancer among women, with nearly 55 000 new cases diagnosed annually; rates are highest in Romania and lowest in Switzerland.[1] The disease burden is greatest in sub-Saharan Africa, southeast Asia, including India, and Latin America.

The positive effect of cervical cancer screening programmes using cytology with and without high-risk human papillomavirus (HPV) DNA testing remains undisputed provided members of the populations served have access to cyclical (ie, repetitive) screening and resources to support intervention when required.[3] Similarly, prophylactic HPV vaccination programmes can only be effective when actively endorsed by health-care providers, advocated by parents, and subject to robust public policy commitment designed to deliver doses to sufficient numbers of at-risk individuals. Patients diagnosed with early invasive disease (eg, International Federation of Gynecology and Obstetrics [FIGO] stage IB_1) might be candidates for fertility-preserving radical trachelectomy with lymphadenectomy or treated effectively with radical hysterectomy with lymphadenectomy plus tailored adjuvant therapy when indicated. In many cases, women who present with locally advanced disease (ie, FIGO stage IB_2 to IVA) might have their tumour eradicated and durably cured in the long term through platinum-based chemoradiation plus high-dose-rate intracavitary brachytherapy.[3,4] However, for patients who present with metastatic disease (ie, FIGO stage IVB), as well as those with non-resectable local recurrence and those who recur at distant sites, treatment options have until most recently been palliative at best. Short-lived responses to platinum-based chemotherapy doublets followed by rapid deterioration of quality of life (QoL) and early death have been the rule, with median survival ranging from 7 months to 12 months in most patients.[3]

On the basis of clinical, pathological, molecular, and therapeutic rationale, vascular endothelial growth factor (VEGF) has emerged as an important therapeutic target to prevent tumour angiogenesis, a process that drives HPV-mediated cervical carcinogenesis. The rationale to target angiogenesis in advanced cervical cancer is based on four observations. Clinically, women with abnormal Papanicolaou cervical cytological screening tests will often be shown to have vascular markings according to cervical colposcopy, which represent harbours of angiogenesis and the beginnings of microinvasive

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disease.[5] Pathologically, a high microvessel intratumoural density of the endothelial cell antigen CD31 predicts a poor prognosis among women diagnosed with invasive cervical cancer.[6] Molecularly, the consequences of viral integration into host DNA activates a cascade through which the human papilloma viral oncoprotein E6 degrades the cellular tumour suppressor gene product p53, while the human papilloma viral oncoprotein E7 inactivates the tumour suppressor gene product retinoblastoma. This cascade ultimately leads to increased hypoxia-inducible factor α expression and increased VEGF production, which promotes angiogenesis.[7] Finally, therapeutically, evidence of antiangiogenesis activity in women with advanced cervical cancer can be found in a phase one trial[8] of an *Aspergillus fumigatus fresenius*-derived angioinhibitory molecule, TNP-470, and phase 2 trials of the anti-VEGF fully humanised monoclonal antibody bevacizumab[9] and the oral small-molecule VEGF receptor tyrosine kinase inhibitor pazopanib.[10]

On Feb 7, 2013, the National Cancer Institute issued a press release[11] indicating that combination of the anti-VEGF monoclonal antibody bevacizumab with two chemotherapy doublets significantly improved overall survival (OS) at the second interim analysis (in 2012) of 271 deaths in the phase 3 randomised controlled Gynecologic Oncology Group (GOG) 240 trial (overall survival of 17·0 months in the chemotherapy plus bevacizumab group *vs* 13·3 months in the chemotherapy-alone group; hazard ratio [HR] 0·71 [98% CI 0·54–0·95]; p=0·004).[12] Within 1 month of formal publication of these interim results, on March 10, 2014, the UK's Cancer Drug Fund approved bevacizumab in combination with chemotherapy for women in England with recurrent or metastatic cervical cancer. This approval was followed by US Food and Drug Administration approval on Aug 14, 2014, and listing of both bevacizumab-containing triplet regimens studied in GOG 240 as Category 1 in the National Comprehensive Cancer Network Cervical Cancer Treatment Guidelines.[13] After public disclosure of the final analysis of the GOG 240 trial at the European Society for Medical Oncology 2014 Congress,[14] regulatory approval of bevacizumab for cervical cancer on the basis of the GOG 240 trial was granted by health authorities in at least 60 countries on six continents.[15,16] In this study we present the final prespecified OS analysis, postprogression overall survival, and final adverse events (AEs) of the GOG 240 trial.

Methods

Study design and participants

In this randomised, controlled, open-label, phase 3 trial (GOG 240), we recruited patients from 81 centres in the USA, Canada, and Spain through the GOG and Spanish Ovarian Cancer Group. Eligible patients had metastatic (FIGO stage IVB), persistent, or recurrent cervical carcinoma. Patients with recurrent disease must not have been candidates for curative therapy via pelvic exenteration. GOG performance status scores of 0 (fully active) or 1 (restricted in physically strenuous activities, but ambulatory) were required, patients had to have adequate renal, hepatic, and bone marrow function, and if thromboembolism was present, it had to have been adequately anticoagulated. Patients also needed to have a urine protein to creatinine ratio of less than 1. All patients must have had measurable disease. Patients must also have recovered from the effects of surgery, radiation therapy, or chemoradiotherapy and be free of active infection requiring antibiotics. Patients receiving chemotherapy for recurrence and those with non-healing wounds or active bleeding conditions were ineligible.

This trial was ethically and scientifically approved by the NCI's Central Institutional Review Board and the local Institutional Review Boards of the GOG-affiliated medical centres throughout the USA and Canada, and the Spanish Ovarian Cancer Group-affiliated hospitals in Spain, where the trial was done. All patients provided written informed consent at enrolment.

Randomisation and masking

Through NCI computer-generated randomisation, we randomly assigned patients 1:1:1:1 (blocking used; block size of four) to one of four treatment regimens, stratified by GOG performance status (0 *vs* 1), previous radiosensitising platinum-based chemotherapy, and disease status (recurrent or persistent *vs* metastatic). Treatment was given open label, but those assessing outcomes were masked.

Procedures

Control chemotherapy treatment consisted of cisplatin (50 mg/m² on day 1 or 2) plus paclitaxel (135 mg/m² or 175 mg/m² on day 1) in 21 day cycles. The non-platinum doublet chemotherapy regimen consisted of topotecan (0·75 mg/m² days 1–3) plus paclitaxel (175 mg/m² on day 1), also in 21 day cycles. We studied each chemotherapy regimen with and without intravenous bevacizumab (15 mg/kg day 1), forming a total of four treatment groups. We discontinued treatment at onset of disease progression or occurrence of unacceptable toxic effects (including fistula or thromboembolism), voluntary withdrawal by the patient, or complete response.

We assessed disease and measured tumours using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. All cancers had central pathology review by the GOG Pathology Committee. We monitored safety according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 during each cycle. AEs were reported until 30 days after the last study treatment. We modified the bevacizumab dose only when weight of the patient changed by more

than 10%. If we held chemotherapy for low absolute neutrophil count or thrombocytopenia, we also held bevacizumab. Bevacizumab could be delayed or discontinued depending on the occurrence, duration, and severity of uncontrolled hypertension (systolic blood pressure of >150 mm Hg or diastolic blood pressure of >100 mm Hg), proteinuria (urine protein to creatinine ratio of ≥3·5), arterial or venous thrombosis, coagulopathy, and intestinal obstruction or disruption. After discontinuation of treatment, we assessed disease every 3 months for 2 years, followed by every 6 months for 3 years until progression. We used three validated and sensitive instruments to measure health-related QoL.

We measured outcomes on five different occasions, four of which had been prespecified (first interim analysis [in 2012], patient-reported outcomes, final analysis, and adverse events) and one of which was planned during the conduct of the trial (second interim analysis [in 2012][12]). The first and second interim analyses are described in the appendix. We provided bevacizumab to patients in the chemotherapy-alone groups when we established that the study had met its primary endpoint at the second interim analysis. We analysed these patients who crossed over to the bevacizumab groups in the chemotherapy-alone groups for final OS and progression-free survival (PFS) analysis as per intention to treat.

See Online for appendix

Outcomes

Primary endpoints were OS based on a pooled analysis of the chemotherapy treatment groups with and without bevacizumab and the frequency and severity of AEs, centrally assessed at the second interim and final analysis by the Data and Safety Monitoring Board (DSMB). We defined OS as the time from randomisation to death or date last seen. Secondary endpoints were to compare PFS and objective tumour responses. We defined PFS as the time from randomisation until the patient had disease progression or died, or if censored, until the date last seen. We defined progression using modified RECIST version 1.0—ie, a 20% increase in the sum of the target lesions' longest dimensions, taking the nadir value during the study as a reference; observation of new lesions; or a decrease in health status due to worsening of disease.

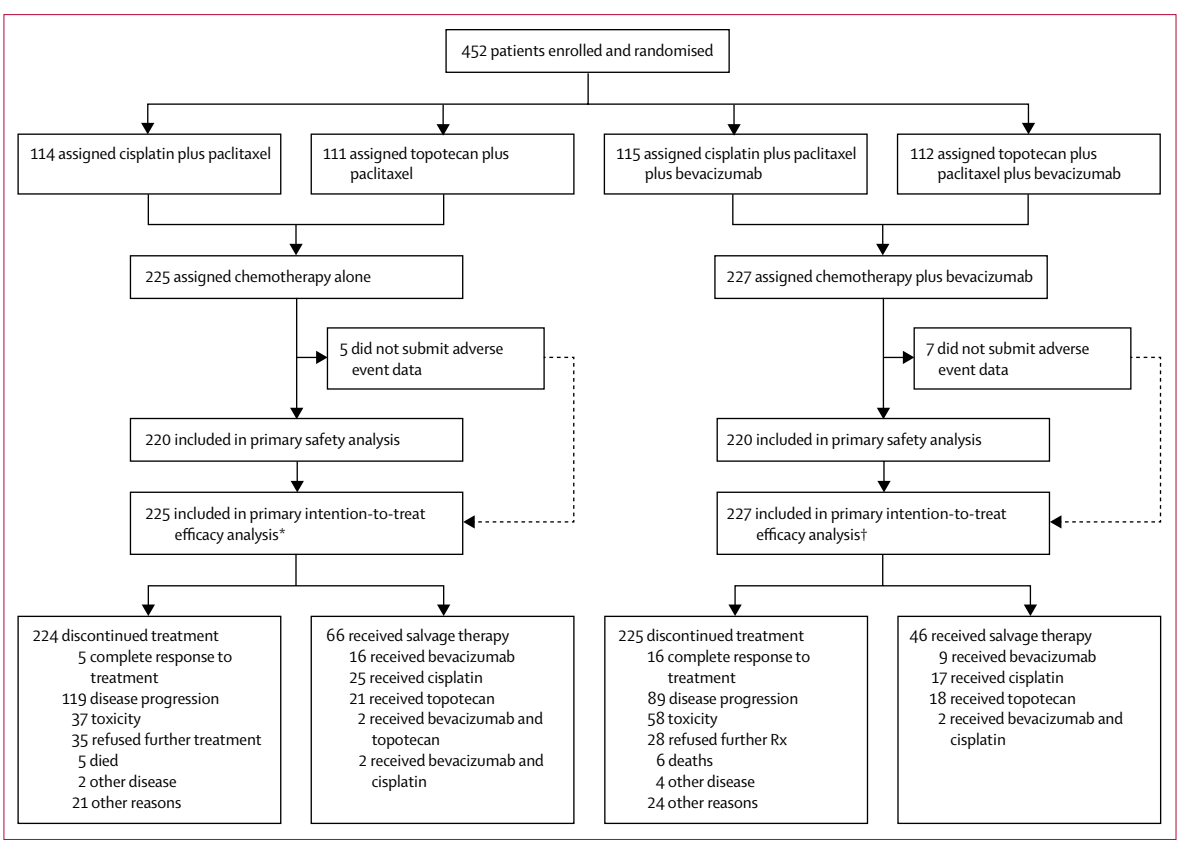

Figure 1: **Trial profile**
12 additional patients in the chemotherapy plus bevacizumab groups and nine additional patients in the chemotherapy-alone groups also achieved a complete response but continued on therapy beyond the complete response for an optional one to two additional cycles as permitted in a modification to the protocol on July 26, 2010. *206 (92%) patients were assessable for the progression-free survival secondary endpoint and 178 (79%) died. †199 (88%) patients were assessable for the progression-free survival secondary endpoint and 170 (75%) died.

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Tertiary endpoints were a QoL component, prospective validation of poor prognostic markers identified in pooled analyses from previous studies,[17] the prevalence of active smoking, the prevalence of tobacco or nicotine dependence and its effect on PFS and OS, and several novel translational endpoints involving circulating tumour cells and VEGF isoform expression.

Statistical analysis

Assuming absence of interaction between experimental agents, the study used a 2×2 factorial design to investigate the ability of either anti-VEGF therapy (bevacizumab; factor A) or a regimen using a non-platinum chemotherapy doublet (topotecan plus paclitaxel; factor B) to significantly affect outcomes. Cisplatin plus paclitaxel served as the control group. The study used the intention-to-treat principle. We assessed safety in patients who received any treatment and submitted AE information.

We accrued a sample size of approximately 450 patients to potentially observe 346 deaths in the final analysis to provide a study with 90% power when either factor was capable of reducing the hazard of death by at least 30%, while limiting the one-sided type I error for each to 2·5% (with an experiment-wise error proportion of no greater than 5%). We scheduled the first interim analysis at near 173 deaths to no longer study a factor or stop the study for futility or report regimen activity early according to the spending function in the event of substantial improvement in survival. Since we designed the study with futility rules, we listed the alternative hypotheses, critical regions, and p values for the primary analyses of efficacy as one-sided.

We assessed differences in OS and PFS by factor level primarily with the log-rank test, stratified by clinical prognostic markers and the level of the other factor. We estimated HRs with a Cox proportional hazards model. To monitor unacceptable toxicity, we embedded two two-stage sequential toxicity analyses early in the conduct of the study (ie, for the first 50 patients assigned to investigational treatment), with specific guidelines dictating when a meeting of the DSMB would need to be convened. The DSMB did the first and second interim analyses and the final analysis. After each analysis, the DSMB released the results to the NRG Oncology Protocol 240 Investigators. We assumed the distribution of the number of severe AEs to be binomial and used group sequential methods to assess whether the probability of a severe AE was low enough to be safe or too high. We assessed changes in health-related QoL using a mixed model for analysis of repeated measures. SAS version 9.4 was used for all analyses. This trial is registered with ClinicalTrials.gov, number NCT00803062.

Role of the funding source

The study's DSMB was comprised of scientists employed by the funder. The funder did not write the manuscript or decide where it should be submitted. The funder approved the study design. Collected data was provided to the funder for database upload. The DSMB analysed and interpreted data. The funder's Cancer Therapeutics Evaluation Program reviewed and approved the final version of the manuscript before submission. KST, MWS, FBS, and BJM had full access to all the data in the study after the data analysis and interpretation by the DSMB had been completed. The decision to submit for publication was made by the corresponding author and approved by all other authors and the NRG Oncology Publications Committee.

Results

Between April 6, 2009, and Jan 3, 2012, we enrolled 452 patients (225 [50%] in the two chemotherapy-alone groups and 227 [50%] in the two chemotherapy plus bevacizumab groups; figure 1). On March 7, 2014, with 348 deaths, the prespecified 346 deaths had been exceeded. Patients were well matched for GOG performance status, ethnicity, histology, disease status,

	Chemotherapy alone (n=225)	Chemotherapy plus bevacizumab (n=227)
Age (years)	46·5 (12·1)	48·9 (11·7)
Histology		
Squamous	152 (68%)	158 (70%)
Unspecified adenocarcinoma	44 (20%)	42 (19%)
Other	29 (13%)	27 (12%)
Race		
White	180 (80%)	171 (75%)
African American	24 (11%)	36 (16%)
Asian	7 (3%)	12 (5%)
Pacific Islander	1 (<1%)	0
Other	13 (6%)	8 (4%)
Disease presentation		
Recurrent	165 (73%)	160 (70%)
Persistent	23 (10%)	28 (12%)
Metastatic	37 (16%)	39 (17%)
GOG performance status		
0	131 (58%)	132 (58%)
1	94 (42%)	95 (42%)
Previous platinum-based radiosensitising chemotherapy	166 (74%)	171 (75%)
Pelvic disease	120 (53%)	123 (54%)
Previous pelvic RT		
Yes	180 (80%)	181 (80%)
No	45 (20%)	46 (20%)
Target lesion in RT zone		
Yes	94 (42%)	85 (37%)
No	130 (58%)	140 (62%)
Unknown	1 (<1%)	2 (1%)

Data are median (SD) or n (%). GOG=Gynecologic Oncology Group. RT=radiotherapy.

Table 1: **Baseline characteristics**

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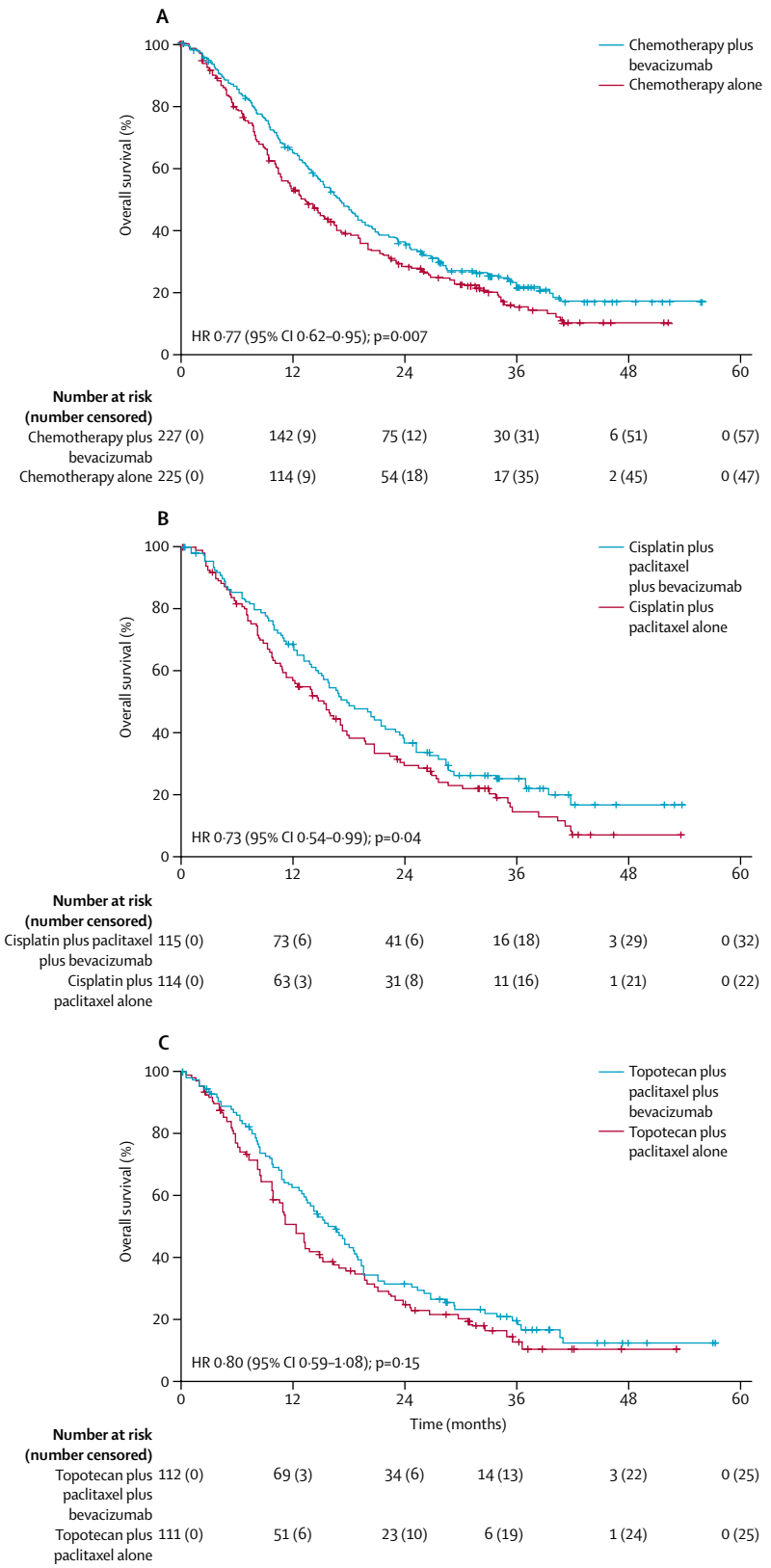

and in-field pelvic recurrences (table 1). Importantly, 337 (75%) of 452 patients had previously received platinum-based radiosensitising chemotherapy, and this proportion was also evenly distributed between those receiving the two chemotherapy regimens.

Between the second interim analysis and final analysis, 20 (9%) patients who had been randomly assigned to the chemotherapy-alone groups crossed over to receive salvage therapy with bevacizumab after progression or crossed over to bevacizumab treatment when the study was known to have met its primary endpoint and provisions to supply bevacizumab to patients in the chemotherapy-alone groups had been made (figure 1).

In the final analysis of OS, chemotherapy plus bevacizumab continued to show a significant improvement compared with chemotherapy alone: 16·8 months versus 13·3 months (HR 0·77 [95% CI 0·62–0·95]; p=0·007; 170 [75%] of 227 patients had an event *vs* 178 [79%] of 225; figure 2). When compared with the cisplatin plus paclitaxel chemotherapy regimen, addition of bevacizumab reduced the hazard of death (OS of 17·5 months in the cisplatin plus paclitaxel plus bevacizumab group *vs* 15·0 months in the cisplatin plus paclitaxel group; 83 [72%] of 115 patients had an event *vs* 92 [81%] of 114; figure 2). We noted no significant difference in OS between the topotecan plus paclitaxel plus bevacizumab group and the topotecan plus paclitaxel-alone group (16·2 months *vs* 12·0 months; 87 [78%] of 112 *vs* 86 [77%] of 111; figure 2). Final OS of patients who had not previously received pelvic radiotherapy was 24·5 months in the chemotherapy plus bevacizumab group versus 16·8 months in the chemotherapy-alone group (HR 0·64 [95% CI 0·37–1·10; p=0·11; 24 [52%] of 46 previously unirradiated patients in the chemotherapy plus bevacizumab groups had an event *vs* 34 [76%] of 45 unirradiated patients in the chemotherapy-alone groups; appendix).

Postprogression OS was 8·4 months in the chemotherapy plus bevacizumab group versus 7·1 months in the chemotherapy-alone group (143 [83%] of 172 had an event *vs* 153 [85%] of 181; figure 3). For patients in the cisplatin plus paclitaxel plus bevacizumab group, postprogression OS was 8·3 months (70 [82%] of 85) versus 6·2 months in the cisplatin plus paclitaxel-alone group (80 [87%] of 92; figure 3). For those in the topotecan plus paclitaxel plus bevacizumab group, postprogression OS was 8·7 months (73 [84%] of 87) versus 7·5 months (73 [82%] of 89) in the topotecan plus paclitaxel-alone group (figure 3).

Final PFS data also showed that bevacizumab plus chemotherapy continued to significantly reduce the

Figure 2: **Overall survival**
Overall survival of the (A) chemotherapy-alone compared with chemotherapy plus bevacizumab groups, (B) cisplatin plus paclitaxel-alone group compared with the cisplatin plus paclitaxel plus bevacizumab group, and (C) topotecan plus paclitaxel-alone group compared with the topotecan plus paclitaxel plus bevacizumab group. Crosses denote censored patients. HR=hazard ratio.

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hazard of progression compared with chemotherapy alone (PFS of 8·2 months *vs* 6·0 months; HR 0·68 [95% CI 0·56–84; p=0·0002; 199 [88%] of 227 patients had an event *vs* 206 [92%] of 225; appendix). We documented complete and partial (overall) responses in 112 (49%) of 227 patients in the chemotherapy plus bevacizumab group versus 80 (36%) of 225 in the chemotherapy-alone group (p=0·003; table 2; appendix). We documented complete and partial responses in 58 (50%) of 115 patients receiving cisplatin plus paclitaxel plus bevacizumab, 54 (48%) of 112 receiving topotecan plus paclitaxel plus bevacizumab, and 52 (46%) of 114 receiving cisplatin plus paclitaxel alone as compared with 28 (25%) of 111 receiving topotecan plus paclitaxel alone (p=0·0004). Because the interaction term is significant, the effect of bevacizumab on the proportion of those responding depends on whether the regimen contains cisplatin or topotecan. Although bevacizumab significantly affects OS and PFS, it has a greater effect on response when given with topotecan plus paclitaxel than with cisplatin plus paclitaxel. Specifically, the proportion of patients with an overall response to topotecan plus paclitaxel is almost doubled when bevacizumab is incorporated into treatment.

32 (15%) of 220 patients in the chemotherapy plus bevacizumab group had fistulas (table 3), all of whom had had previous radiotherapy, compared with three (1%) in the chemotherapy-alone group, also all of whom had had previous radiotherapy. 13 (6%) patients had clinically significant or severe (ie, grade 3) fistula in the chemotherapy plus bevacizumab group versus one (<1%) in the chemotherapy-alone group. No fistulas resulted in surgical emergencies, sepsis, or death, and in addition to pelvic irradiation, other factors associated with fistulas included pelvic disease, pre-existing hypertension, and current tobacco use (Willmott L, Biltmore Cancer Center, Phoenix, AZ, USA, personal communication). Analyses of these factors are ongoing and will be presented elsewhere. All adverse events of any grade are listed in the appendix.

In an exploratory post-hoc landmark OS analysis of those who had received bevacizumab, the occurrence of grade 2 or higher neutropenia was associated with improved OS (14·6 months in those with grade <2 neutropenia *vs* 17·5 months in those with grade ≥2 neutropenia; HR 0·75 [95% CI 0·60–0·93]; p=0·009; appendix), suggesting that neutropenia could represent a surrogate biomarker of survival. Conversely, development of grade 3 or higher thromboembolism or fistula might be associated with a survival disadvantage (appendix). Quality of life[18] and prospective validation of poor prognostic markers[19] results have been previously published. Tobacco or nicotine dependence and translational endpoint results are still being analysed and will be reported elsewhere.

Discussion

Clinical, histopathological, and molecular evidence supports targeting of angiogenesis in advanced cervical cancer.[3,8–10,20] Sequestration of VEGF with use of bevacizumab when combined with chemotherapy led to a significant and, in our opinion, clinically meaningful survival advantage among women with advanced cervical cancer in this phase 3 randomised controlled trial. Final analysis of this study is noteworthy in having taken place nearly 26 months after randomisation of the last patient in the trial. Continued separation of the OS curves at final analysis indicates that the survival benefit conferred by incorporation of bevacizumab identified at

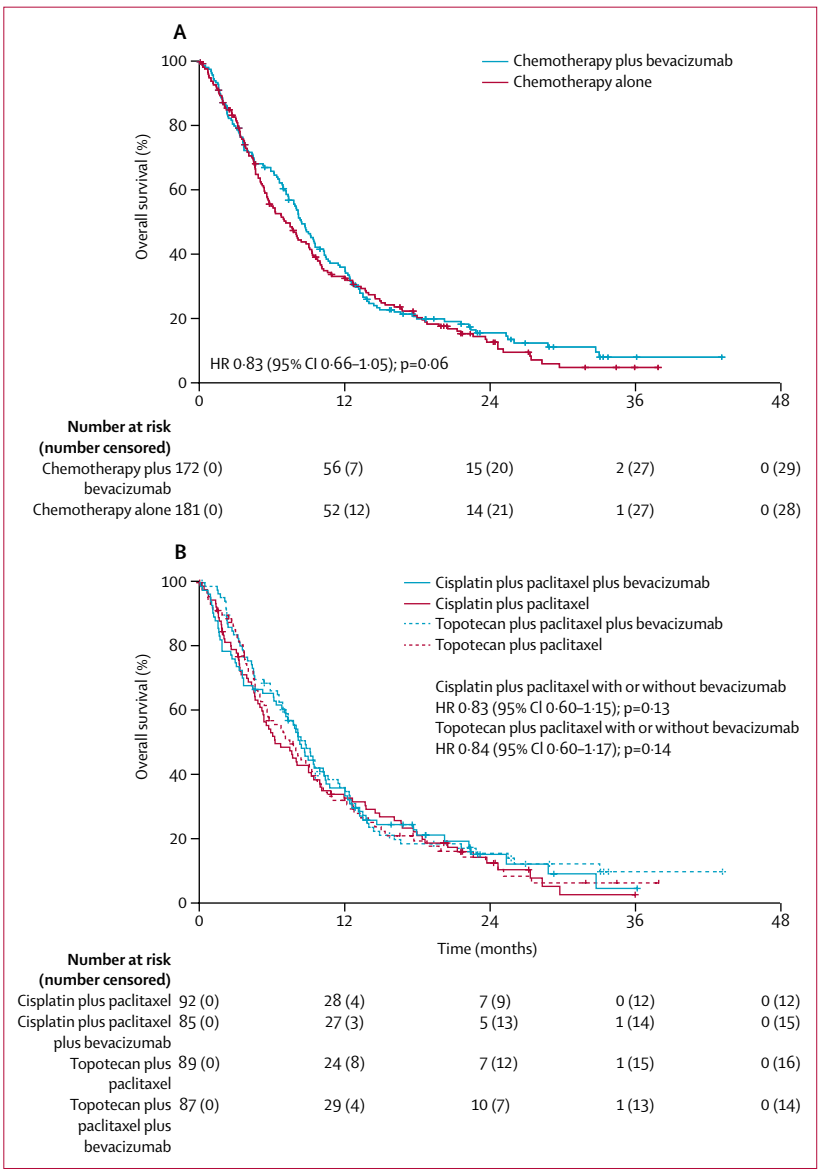

Figure 3: **Postprogression overall survival**
(A) Chemotherapy alone versus chemotherapy plus bevacizumab. (B) Cisplatin plus paclitaxel with and without bevacizumab and topotecan plus paclitaxel with and without bevacizumab. Crosses denote censored patients. HR=hazard ratio.

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	Cisplatin plus paclitaxel (n=114)	Cisplatin plus paclitaxel plus bevacizumab (n=115)	Topotecan plus paclitaxel (n=111)	Topotecan plus paclitaxel plus bevacizumab (n=112)	Total (n=452)
Complete response	11 (10%)	18 (16%)	6 (5%)	13 (12%)	48 (11%)
Partial response	41 (36%)	40 (35%)	22 (20%)	41 (37%)	144 (32%)
Stable disease	45 (39%)	42 (37%)	54 (49%)	43 (38%)	184 (41%)
Progressive disease	12 (11%)	7 (6%)	21 (19%)	6 (5%)	46 (10%)
Indeterminate	5 (4%)	8 (7%)	8 (7%)	9 (8%)	30 (7%)

Data are n (%).

Table 2: **Tumour response**

	Chemotherapy alone (n=220)	Chemotherapy plus bevacizumab (n=220)	Risk ratio	p value
Grade 2 genitourinary fistula	1 (<1%)	8 (4%)	8·00 (1·01–63·43)	0·04
Grade 3 genitorurinary fistula	1 (<1%)	6 (3%)	6·00 (0·73–49·43)	0·12
Grade 2 GI fistula	1 (<1%)	11 (5%)	11·00 (1·43–84·48)	0·006
Grade 3 GI fistula	0	7 (3%)	NA	0·02
Grade 2 or higher hypertension	4 (2%)	55 (25%)	13·75 (5·07–37·29)	0·001
Grade 4 or higher neutropenia	58 (26%)	80 (36%)	1·37 (1·04–1·83)	0·03
Grade 3 or higher febrile neutropenia	12 (5%)	12 (5%)	1·00 (0·46–2·18)	1
Grade 3 or higher GI bleeding	1 (<1%)	4 (2%)	4·00 (0·45–35·50)	0·37
Grade 3 or higher proteinuria	0	5 (2%)	NA	0·06
Grade 3 or higher thrombosis or embolism	4 (2%)	18 (8%)	4·50 (1·55–13·08)	0·004
Grade 2 or higher pain	63 (29%)	72 (33%)	1·14 (0·86–1·51)	0·41

Data are n (%) or risk ratio (95% CI). GI=gastrointestinal. NA=not applicable.

Table 3: **Adverse events**

the second interim analysis[12] was not transient. At longer than 50 months of maximum follow-up, many patients continue to benefit from stable disease, and some have been cured with no evidence of clinical and radiological disease. Clearly first-line therapy using bevacizumab in the recurrent, persistent, or metastatic setting has clinical value, as the OS curves do not converge at the final analysis, despite having 20 patients initially randomly allocated to the chemotherapy-alone groups crossing over to receive salvage therapy with bevacizumab. Given that advanced cervical cancer is a disease for which OS has been typically measured in months (eg, 7–12 months at best), these data indicate that antiangiogenesis therapy can have clinically meaningful therapeutic benefit in this population.

Clinically significant fistula (ie, grade 3, requiring intervention) occurred in 13 (6%) patients receiving bevacizumab, all of whom had been previously irradiated. Analysis of the magnitude of risk conferred by additional clinical factors (eg, concurrent tobacco use, pre-existing hypertension, and pelvic tumour) is underway. Unlike the surgical emergencies that manifest when gastrointestinal perforation occurs among women with ovarian cancer who receive bevacizumab, none of the fistulae in this study required urgent surgical intervention or resulted in sepsis or death. Importantly, prospective validation of the Moore clinical criteria[17] in this trial provides oncologists with the first scoring system for cervical cancer, which can be used to estimate response and survival and potentially identify patients who are best treated without bevacizumab (eg, a preirradiated patient at risk of fistula for whom the survival benefit attributable to addition of bevacizumab is negligible).[19] Late injury of radiotherapy is microvascular and therefore preirradiated patients being considered for treatment with chemotherapy plus bevacizumab should be informed that the risk of vascular complications could be increased.

Through highly stringent and rigid eligibility criteria not previously used by the GOG in previous therapeutic trials of advanced cervical cancer, the study population was effectively sanitised. Specifically, by restricting GOG performance status to 0 or 1, requiring normal renal function, correction of malnutrition, optimisation of medical comorbidities, and control of tumour-related pain, the GOG 240 population represented the so-called healthiest cohort of a population with a very poor prognosis. We felt this restriction to be necessary to effectively position the factors being investigated (bevacizumab and substitution of topotecan for cisplatin) for the best chance for success. Although clearly conjecture at this point, these restrictions on eligibility for trial participation could have contributed to development of a control group that did not underperform and QoL scores which, based on three independent previously validated QoL instruments, did not deteriorate significantly when antiangiogenesis therapy was added to either chemotherapy regimen.[18] The message that emerges is one of medicine first and oncology second in that women with advanced cervical cancer are best served when physicians emphasise medical management before dispatching the oncological armamentarium.

As per the first interim analysis findings, substitution of topotecan for cisplatin did not circumvent suspected acquired drug resistance to platinum that might have occurred when patients received platinum-based chemoradiation before recurrence.[12] This finding suggests that the issue is not one of platinum resistance per se but rather chemotherapy resistance in general. However, as much as GOG 240 is seen as an antiangiogenesis therapy trial, it is also a study that shows the proof of principle and value of systemic therapy.[13,21] The magnitude of efficacy benefit conferred by bevacizumab is similar regardless of which chemotherapy doublet it is combined with. Since the Japanese Clinical Oncology Group phase 3 non-inferiority trial[22] of cisplatin plus paclitaxel versus carboplatin plus paclitaxel showed significant non-inferiority, several centres have considered a carboplatin plus paclitaxel backbone to combine with bevacizumab. On the basis of subset analyses from the Japanese trial, a

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survival advantage in the cisplatin group was observed among women who had not previously received cisplatin as part of primary chemoradiation for locally advanced disease. Therefore, the cisplatin plus paclitaxel plus bevacizumab triplet might be preferable for patients who are previously untreated with cisplatin, as well as the elderly and those who have received previous extended-field irradiation, for whom diminished bone marrow reserves would render carboplatin prohibitive.

Following this line of reasoning, the finding that on analysis of prognostic factors,[12] the significant survival benefit conferred by bevacizumab was sustained, even when the disease was in the previously irradiated pelvis, is remarkable. Clearly delivery of antibody to an anatomical region with presumed radiation-induced vascular compromise is possible. Together with the observations at final analysis that OS and PFS remain significantly improved among those randomly allocated to the bevacizumab groups, GOG 240 shows a proof of concept of antiangiogenesis therapy in this disease.[23] This proof of concept, in turn, suggests that bevacizumab monotherapy deserves some consideration, particularly among patients intolerable to antineoplastic therapy, despite several dose reductions ultimately requiring peeling back of chemotherapy.

Antiangiogenesis therapy has also been shown to be effective in other gynaecological cancers. Eight phase 3 randomised trials assessing five different agents in newly diagnosed and recurrent ovarian cancer have been done, all of which met their primary endpoint (ie, PFS), and a ninth trial met its secondary endpoint (ie, PFS).[24] Many investigators hypothesise that the inability to show an OS benefit with antiangiogenesis therapy in ovarian cancer is due to the fact that the disease is chemosensitive, and because postprogression therapy cannot be controlled, the ability to show an OS benefit with antiangiogenesis therapy becomes difficult. Conversely, cervical cancer is chemoresistant and therefore an OS benefit with a therapy (eg, antiangiogenesis treatment) that has activity in the advanced cervix population might be easier to show than for ovarian cancer because these patients are unlikely to receive multiple lines of chemotherapy. However, an alternative explanation has emerged that suggests that because ovarian cancer is characterised by genomic instability, it is a more heterogeneous disease than is cervical cancer. Cervical cancer is driven by HPV infection, resulting in a homogeneous tumour, characterised by viral oncogene-driven angiogenesis.[16] Although clearly conjecture, VEGF inhibition could possibly result in an OS benefit in cervical cancer and not in ovarian cancer because bevacizumab is more effective in cervical cancer than in ovarian cancer. Gourley and colleagues[25] from the UK identified an immune subgroup in ovarian cancer that does not respond to bevacizumab and at least two proangiogenic subgroups for which PFS is improved with bevacizumab therapy.

Two important issues are generated by the final OS analysis. Although the drug has been approved for advanced cervical cancer in many countries, it is not being provided by various governments and ministries of health for all patients who are candidates for treatment. In most countries, only those who can afford bevacizumab are able to receive it. This inadequate provision is also true in so-called developing countries, which are in fact not developing, but rather remaining the same.

We acknowledge that regulatory approval of a drug for a specific indication by a country's health agency does not indicate that the drug will be provided to all affected citizens. This shortfall is particularly true when drugs deemed to be costly are considered. US FDA approval was actually preceded by Cancer Drug Fund approval in England. Unlike the National Institute of Health and Care Excellence, the Cancer Drug Fund focuses on making drugs available that are deemed to not be cost-effective. A Markov analysis[26] using data from this trial indicated that bevacizumab becomes cost-effective with a 75% reduction in cost. This finding suggests that part of the solution to provision of antiangiogenesis therapy might lie in the upcoming expiration of the bevacizuamb patent from 2019 to 2022 in various countries and introduction of biosimilars. Biosimilars to monoclonal antibodies might be difficult to generate, however.

An issue created by GOG 240 is a new patient population; specifically, women with advanced cervical cancer who progress after treatment with bevacizumab. Although we did not observe a rebound effect (ie, shorter survival after bevacizumab is stopped than after chemotherapy alone is stopped) in our analysis of postprogression survival, the question of which therapies to study in the second-line setting still remains. Other antiangiogenesis agents such as cediranib should be studied, particularly in light of the activity reported by Symonds and colleagues[27] and Luvero and colleagues[28] in this population. Non-VEGF-dependent angiogenesis inhibitors (eg, the angiopoietin axis inhibitor trebananib) and vascular-disrupting agents that target existing tumour vasculature might also be considered. Given the immunological dysfunction that prevents viral clearance in women who develop cervical cancer, immunological-based therapies are promising and a *Listeria monocytogenes*-based HPV 16 E7 therapeutic vaccine (ADXS-HPV), autologous T-cell therapy, and the antiprogrammed cell death 1 immunomodulators nivolumab and pembrolizumab are being investigated.[29,30] Signal transduction pathways relevant to cervical carcinogenesis that can be targeted include the phosphoinositide 3 kinase-protein kinase B-mammalian target of rapamycin pathway, homologous recombination deficiency pathways that can exploit synthetic lethality, and the Notch binary cell fate decision pathway.[29,31] Finally, adenoviral-directed gene therapy to reconstitute wild-type p53 function or suicide genes, and identification and targeting of cervical cancer stem cells, might also represent viable therapeutic options in the future.

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To be able to even discuss new therapies in advanced cervical cancer is a statement that some progress has finally been made. The GOG has now completed nine phase 3 randomised trials over three decades in this population[12] and with this final OS analysis of the ninth trial (ie, GOG 240), we have at last placed the proverbial foot in the door. With some ground gained, the challenge exists to identify tolerable treatments that can extend survival further. Upcoming trials will probably emphasise different classes of antiangiogenesis agents, immune modulators and checkpoint inhibitors, chemotherapy-free combinations, and translational science.

Contributors

KST was the study chair and principle investigator and BJM was the disease site chair (ie, Cervical Cancer Committee Chair of NRG Oncology). KST, MWS, MFB, RTP, PJD, LJC, WTC, FBS, RAB, JTT, MJB, SEW, DHM, W-JK, and BJM, designed and carried out the study. All authors interpreted data. HH analysed quality of life data and HEM was the pathologist. KST, BJM, LMR, LML, AO, TJR, and MML enrolled patients. KST wrote the original manuscript and subsequent revisions, which were reviewed by all other authors. KYL provided extensive critical insight and revisions for all drafts of the manuscript.

Declaration of interests

KST, MFB, and BJM report that their institutions and the Gynecologic Oncology Group received grants from Genentech to do this clinical trial. KST, RAB, and BJM report that they have participated on an advisory board for Genentech and KST and BJM report that they have served as a speaker on a round table discussion of bevacizumab and two continuing medical education-accredited symposia on bevacizumab for Genentech. BJM and JTT have served on a Genentech speaker's bureau. RTP reports that he received previous clinical trial funding from Genentech and Roche. All other authors declare no competing interests.

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