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Improved Survival with Bevacizumab in Advanced Cervical Cancer

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Abstract

Background—Vascular endothelial growth factor (VEGF) promotes angiogenesis, a mediator of disease progression in cervical cancer. Bevacizumab, a humanized anti-VEGF monoclonal antibody, has single-agent activity in previously treated, recurrent disease. Most patients in whom recurrent cervical cancer develops have previously received cisplatin with radiation therapy, which reduces the effectiveness of cisplatin at the time of recurrence. We evaluated the effectiveness of bevacizumab and nonplatinum combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer.

Methods—Using a 2-by-2 factorial design, we randomly assigned 452 patients to chemotherapy with or without bevacizumab at a dose of 15 mg per kilogram of body weight. Chemotherapy consisted of cisplatin at a dose of 50 mg per square meter of body-surface area, plus paclitaxel at a dose of 135 or 175 mg per square meter or topotecan at a dose of 0.75 mg per square meter on days 1 to 3, plus paclitaxel at a dose of 175 mg per square meter on day 1. Cycles were repeated every 21 days until disease progression, the development of unacceptable toxic effects, or a complete response was documented. The primary end point was overall survival; a reduction of 30% in the hazard ratio for death was considered clinically important.

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Results—Groups were well balanced with respect to age, histologic findings, performance status, previous use or nonuse of a radiosensitizing platinum agent, and disease status. Topotecan–paclitaxel was not superior to cisplatin–paclitaxel (hazard ratio for death, 1.20). With the data for the two chemotherapy regimens combined, the addition of bevacizumab to chemotherapy was associated with increased overall survival (17.0 months vs. 13.3 months; hazard ratio for death, 0.71; 98% confidence interval, 0.54 to 0.95; P = 0.004 in a one-sided test) and higher response rates (48% vs. 36%, P = 0.008). Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of hypertension of grade 2 or higher (25% vs. 2%), thromboembolic events of grade 3 or higher (8% vs. 1%), and gastrointestinal fistulas of grade 3 or higher (3% vs. 0%).

Conclusions—The addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median overall survival. (Funded by the National Cancer Institute; GOG 240 ClinicalTrials.gov number, NCT00803062.)

Rates of cervical cancer in developed countries have decreased dramatically because of cytologic screening and DNA testing for high-risk human papillomavirus (HPV) types. Approximately 12,000 cases of cervical cancer are diagnosed in the United States annually, and with continued increases in HPV vaccination, numbers of cases are expected to decrease further.[1] However, for vulnerable populations without access to health care in the United States and throughout the world, cervical cancer remains a considerable problem, with 500,000 new cases and 250,000 deaths annually.[2] Although early-stage and locally advanced cancers may be cured with radical surgery, chemoradiotherapy, or both, patients with metastatic cancers and those with persistent or recurrent disease after platinum-based chemoradiotherapy have limited options.[3-17] Nonplatinum combination chemo-therapy has been proposed as a strategy to circumvent platinum resistance, but new forms of therapy are needed.

Vascular endothelial growth factor (VEGF) is a key mediator of tumor angiogenesis, a process that correlates directly with the extent of disease and inversely with survival.[18] Bevacizumab, a humanized VEGF-neutralizing monoclonal antibody, has single-agent activity in heavily pretreated, recurrent cervical carcinoma.[19,20] In GOG 240, a phase 3, randomized trial performed in the United States and in Spain through the Gyneco-logic Oncology Group (GOG) and the Spanish Research Group for Ovarian Cancer, we investigated the incorporation of bevacizumab and the use of nonplatinum combination chemotherapy in the treatment of advanced cervical cancer.

Methods

Study Oversight

The study was sponsored by the National Cancer Institute, which provided bevacizumab without charge. All the authors wrote the manuscript and take responsibility for the accuracy and completeness of the reported data and for the fidelity of the study to the protocol, which is available with the full text of this article at NEJM.org.

Patients

Patients with metastatic, persistent, or recurrent cervical carcinoma were eligible for the study. Patients with recurrent disease were excluded if they were candidates for curative therapy by means of pelvic exenteration. All cancers were confirmed by a central pathology laboratory. A GOG performance status score of 0 or 1 (on a scale of 0 to 4, with 0 indicating that the person is fully active and 1 indicating that the person is restricted in physically strenuous activities but ambulatory) was required, and patients had to have adequate renal, hepatic, and bone marrow function. All patients were required to have measurable disease. Patients treated with chemotherapy for recurrence and those with nonhealing wounds, active bleeding conditions, or inadequately anticoagulated thromboembolism were ineligible. All patients provided written informed consent before enrollment.

Study Design and Treatment

Patients were randomly assigned to one of four intravenous regimens that were repeated at 21-day intervals. Control treatment consisted of cisplatin (at a dose of 50 mg per square meter of body-surface area) plus paclitaxel (at a dose of 135 or 175 mg per square meter on day 1). The non-platinum combination chemotherapy consisted of topotecan (at a dose of 0.75 mg per square meter on days 1 to 3) plus paclitaxel (at a dose of 175 mg per square meter on day 1). Each of these regimens was studied with and without bevacizumab (at a dose of 15 mg per kilogram of body weight on day 1). Treatment was discontinued at the onset of disease progression or the development of unacceptable toxic effects, or if the patient had a complete response.

Assessments

Disease was assessed by means of physical examination and chest radiography, as well as by means of computed tomography or magnetic resonance imaging of the abdomen and pelvis within 28 days before the study treatment was initiated. In patients without disease progression, imaging was repeated every other cycle. Tumor measurements according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1, were made within 1 week before the next planned cycle.[21] After discontinuation of treatment, disease was assessed every 3 months for 2 years, followed by assessment every 6 months for 3 years until disease progression was documented.

Three validated, sensitive instruments were used to measure health-related quality of life. The Trial Outcome Index of the Functional Assessment of Cancer Therapy (FACT)–Cervix (FACT-Cx-TOI) survey was used to assess physical and functional well-being (on a scale from 0 to 4, with higher scores indicating worsening well-being). Pain was measured with the use of the Brief Pain Inventory (BPI) (on a scale from 0 to 10, with higher scores indicating more severe pain). Neurotoxicity was measured with the use of the neurotoxicity subscale short form (FACT/GOG-NTX) (on a scale from 0 to 4, with higher scores indicating increased neurotoxicity).[22] Baseline assessments were completed before randomization, before cycles 2 and 5, and 6 and 9 months after cycle 1.

Safety, as assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, was monitored during each cycle.[23,24] Myeloid growth factor

was permitted only for hospitalized patients with grade 3 or higher febrile neutropenia (absolute neutrophil count, <1000 per cubic millimeter and a single temperature measurement higher than 38.3°C [101.0°F] or a sustained temperature of 38.0°C [100.4°F] or higher for more than 1 hour). Subsequent prophylaxis was allowed if febrile neutropenia occurred despite one dose level reduction (see the protocol and Tables S2 through S7 in the Supplementary Appendix, available at NEJM.org). The bevacizumab dose was modified only if the patient's weight changed by more than 10%. If chemotherapy was withheld because of a low absolute neutrophil count or thrombocytopenia, bevacizumab was also withheld. Bevacizumab could be delayed or discontinued depending on the occurrence, duration, and severity of uncontrolled hypertension (systolic blood pressure >150 mm Hg or diastolic blood pressure >100 mm Hg), protein-uria (urine protein-to-creatinine ratio ≥3.5), arterial thrombosis, venous thrombosis, coagulopathy, or intestinal obstruction or disruption.

Statistical Analysis

The statistical analysis plan is available with the protocol at NEJM.org. Assuming an absence of interaction between experimental agents, we used a 2-by-2 factorial design to investigate the effect of anti-VEGF therapy (bevacizumab) and a regimen of nonplatinum combination chemotherapy (topotecan–paclitaxel).[25] The study was based on the intention-to-treat principle. Patients were prospectively stratified according to GOG performance status, prior use or nonuse of radiosensi tizing platinum, and disease status (recurrence or persistence of disease vs. advanced primary disease).

The primary end points were overall survival and the frequency and severity of adverse events associated with each regimen. Progression-free survival and the response rate were secondary end points. Differences in overall survival and progression-free survival according to intervention level were assessed primarily by means of the log-rank test, stratified according to clinical prognostic markers and the level of the other intervention.[26] Hazard ratios were estimated with the use of a Cox proportional-hazards model.[27]

We calculated that we would need to enroll approximately 450 patients, with approximately 346 deaths expected, to provide the study with 90% power to detect a reduction in the risk of death of at least 30% with either experimental treatment, with the one-sided type I error rate limited to 2.5% for each regimen (overall error rate, 5%). An interim analysis, scheduled to be conducted after 173 patients had died, allowed for elimination of one of the experimental treatments or discontinuation of the study for futility or for reporting treatment activity early in the event of dramatic improvement in survival.[28,29] Since the study was designed with futility rules, one-sided tests were specified for the alternative hypotheses, critical regions, and P values.

Adverse events were reported until 30 days after the last dose of study treatment had been administered and were summarized for patients who received any therapy and for whom adverse event information was submitted. Changes in health-related quality of life were evaluated with the use of a mixed model for analysis of repeated measures.[30]

Results

Patients

Between April 2009 and January 2012, a total of 452 women were enrolled from 164 institutions in the United States and Spain. The data freezes occurred on February 6, 2012, and December 12, 2012. Analyses provided in this article concerning the bevacizumab regimens are from the second data freeze. Figure 1 shows randomization and follow-up among patients assigned to chemotherapy with or without bevacizumab.

Demographic characteristics and clinical and pathological factors were evenly distributed between the treatment groups (see Table S15 in the Supplementary Appendix). The majority of patients (72%) had recurrent disease, and 11% of patients had persistent disease. More than 70% of patients in each group had previously received platinum-based chemoradiotherapy.

The median number of cycles for patients treated with chemotherapy alone was 6 (range, 0 to 30), and for those who received chemotherapy plus bevacizumab, the median was 7 (range, 0 to 36). Ninety-seven percent of patients discontinued the study treatment; the most common reason was disease progression (in 51% of patients who received chemotherapy [either regimen] alone and 38% of patients who received chemo-therapy [either regimen] plus bevacizumab). Treatment was discontinued owing to adverse events in a higher percentage of patients in the chemotherapy–bevacizumab group than in the chemotherapy-alone group (25% vs. 16%).

Efficacy

At the time of the interim analysis (the first data freeze), 62% of patients were alive, with a median follow-up of 12.5 months. As compared with cisplatin–paclitaxel (either with or without bevacizumab) topotecan–paclitaxel was associated with a significantly higher risk of progression (hazard ratio, 1.39; 95% confidence interval [CI], 1.09 to 1.77) (Fig. 2A), but it did not significantly affect overall survival (hazard ratio for death, 1.20; 99% CI, 0.82 to 1.76) (Fig. 2B). There was also no significant difference in mortality between the chemotherapy regimens in the subgroup of patients with previous exposure to platinum (hazard ratio, 1.18; 95% CI, 0.84 to 1.65) and in the subgroup with no previous exposure to platinum (hazard ratio, 1.35; 95% CI, 0.68 to 2.69) (Fig. S3 and S4 in the Supplementary Appendix). Noting that topotecan was not a superior (or an inferior) substitute for cisplatin, the data and safety monitoring committee voted on March 12, 2012, for early release of data from this first data freeze to all investigators and patients.

At a median follow-up of 20.8 months, 271 deaths had been reported (60% of the total study population), and the results from the second data freeze were partially released after a recommendation by the data and safety monitoring committee. The interaction term was not significant, indicating that there was no interaction between the two treatment regimens under investigation. The incorporation of bevacizumab significantly improved the median overall survival as compared with chemotherapy alone (17.0 months vs. 13.3 months; hazard ratio for death, 0.71; 98% CI, 0.54 to 0.95) (Fig. 3A). A sig nificant improvement in progression-free survival was also seen (8.2 vs. 5.9 months; hazard ratio for disease

progression, 0.67; 95% CI, 0.54 to 0.82) (Fig. 3B). The response rate was significantly higher among patients who received bevacizumab than among those who did not receive bevacizumab (48% vs. 36%) (relative probability of a response, 1.35; 95% CI, 1.08 to 1.68; P = 0.008, two-sided test). Among patients who received bevacizumab, 28 had a complete response, and among those who received chemotherapy alone, 14 had a complete response (P = 0.03). Treatment was discontinued in 21 patients who had a complete response.

Treatment with cisplatin–paclitaxel–bevaciz umab, as compared with cisplatin–paclitaxel alone, was associated with a hazard ratio for death of 0.68 (95% CI, 0.48 to 0.97) (Fig. 3C). The response rates were 50% (cisplatin–paclitaxel–bevacizumab) and 45% (cisplatin–paclitaxel) (P = 0.51, two-sided test); 17 patients and 9 patients had a complete response, respectively. Topotecan–paclitaxel–bevacizumab, as compared with topotecan–paclitaxel alone, was associated with a hazard ratio for death of 0.74 (95% CI, 0.53 to 1.05) (Fig. 3D). The response rates were 47% (topotecan–paclitaxel– bevacizumab) and 27% (topotecan–paclitaxel) (P = 0.002, two-sided test); 11 patients and 5 patients had a complete response, respectively.

Figure 3E shows multiple prognostic factors. The treatment benefit with bevacizumab was also observed in subgroup analyses of age, performance status, race, squamous histologic type, status with respect to prior platinum exposure, recurrent or persistent disease, and pelvic location of the target lesion.

Quality of Life

The rate of compliance with health-related quality of life surveys was 96%, 84%, 78%, 67%, and 63% among patients at cycles 1, 2, and 5, and at 6 months and 9 months of follow-up, respectively, and was balanced between treatment groups (P = 0.67). The mean FACT-Cx-TOI scores exceeded 70 at each time point in each group. The fitted mixed-model estimates for the FACT-Cx-TOI and BPI scores indicated that the addition of bevacizumab did not adversely affect health-related quality of life; scores for patients who received antiangiogenic therapy were 1.2 points lower, on average than scores for patients who did not receive such therapy, although the difference was not significant (99% CI, –4.1 to 1.7; P = 0.30). The fitted mixed-effects mixed-distribution model estimates for the FACT/GOG-NTX scores showed a nonsignificant trend for patients receiving bevaciz umab to report fewer neurotoxic symptoms (overall odds ratio, 0.58; 99% CI, 0.29 to 1.17; P = 0.05), and the severity of neurotoxic symptoms reported was similar in the two groups (P = 0.70).

Safety

Table 1 shows the frequency of adverse events potentially associated with bevacizumab. Hyper-tension of grade 2 or higher was significantly more common with bevacizumab-containing regimens than with regimens that did not con tain bevacizumab (25% vs. 2%, P<0.001), but no patients discontinued bevacizumab because of hypertension. Gastrointestinal or genitourinary fistulas of grade 3 or higher were significantly increased with the bevacizumab-containing regimens (6% vs. 0%, P = 0.002), as were thromboembolic events of grade 3 or higher (8% vs. 1%, P = 0.001). There were no significant differences between the groups in the rates of neutropenia of grade 4 or higher,

febrile neutropenia of grade 3 or higher, and pain of grade 2 or higher. Proteinuria of grade 3 or higher was rare. Gastrointestinal and genitourinary bleeding was uncommon, and clinically relevant central nervous system bleeding did not occur. Fatal adverse events were reported in four patients (1.8%) who received chemotherapy alone and in four patients (1.8%) who received chemotherapy plus bevacizumab (P = 1.0). Tables S17, S18, and S19 in the Supplementary Appendix contain additional details about toxic effects.

Discussion

This study met one of its primary end points; the regimens that included bevacizumab were associated with a reduced hazard of death. This effect was consistent across multiple prognostic subgroups. The control chemotherapy regimen did not underperform, since the median overall survival of 13.3 months among patients receiving this regimen was similar to that observed among patients who received cisplatin–paclitaxel in the preceding phase 3 trial.[5] The bevacizumab-containing regimens were associated with a reduced hazard of disease progression and an increased probability of a response. Even when the target lesions were located in the previously irradiated pelvis, it appears that bevacizumab-containing therapy was effective. Bevacizumab-related adverse events were similar to those reported for other tumor types.[19,20] The survival gains with bevacizumab were not accompanied by any significant reduction in health-related quality of life. Patients who received bevacizumab-containing regimens, as compared with those who received chemotherapy alone, reported fewer neurotoxic symptoms. Significantly higher proportions of patients receiving bevacizumab had gastrointestinal fistulas (3%) and thromboembolic events (8%).

The use of topotecan–paclitaxel was selected on the basis of laboratory data showing synergy between topotecan and microtubule-interfering agents[31] and a phase 2 trial by Tiersten et al.[32] in which the regimen was active in patients who had previously received radiation therapy. Topotecan– paclitaxel did not outperform cisplatin–paclitaxel, even among patients with prior exposure to cisplatin.

Tumor neovascularization is associated with an aggressive course in cervical cancer. Vascular markings seen at colposcopy in women with abnormal Papanicolaou tests are hallmarks for invasive disease, and increased microvessel density and strong immunostaining for the endothelial-cell marker, CD31, in cervical cancers suggest a poor prognosis.[2] VEGF is involved in mitogenesis, angiogenesis, endothelial-cell survival, and induction of hematopoiesis.[33] Patients with high-grade cervical dysplasia and invasive carcinoma have increased expression of VEGF and hypoxia-inducible factor 1α (HIF-1α).[34] The invasive phenotype is present only with up-regulated VEGF. Overexpression of oncogenic HPV subtypes enhances HIF-1α protein accumulation and VEGF expression.

The molecular mechanism through which HPV mediates tumor angiogenesis has been elucidated. In the native form, HPV exists as circular double-stranded DNA episomes, and viral E2 expression prevents transcription of the viral onco-genes, E6 and E7. The E2 reading frame is disrupted on viral integration into host DNA, resulting in lack of repression of E6 and E7, which mediate neoplastic transformation through degradation or inactivation

of cellular tumor-suppressor protein p53 and retinoblastoma protein, respectively.[35] VEGF isoform expression can be considerably reduced by silencing HPV E6 messenger RNA with specific small interfering RNAs but not when p53 is silenced, suggesting that E6 induces VEGF through a p53-independent mechanism.[36] HIF-1α activity enhanced by E7 maps to the C-terminal and correlates with displacement by E7 of the histone deacetylases HDAC1, HDAC4, and HDAC7.[37]

Short-lived responses to chemotherapy in patients with advanced cervical cancer indicate that the disease is relatively chemorefractory. We selected overall survival as the primary end point because, unlike patients with other cancers, patients with advanced cervical cancer usually do not have a sustained response to chemotherapy and cannot receive multiple lines of chemotherapy because of unacceptable side effects. We think that the 3.7-month improvement in median overall survival attributed to the addition of bevacizumab to chemotherapy is clinically meaningful. Antiangiogenic therapy and possibly other targeted agents may provide additional gains in survival time, allowing for multiple lines of therapy with sustained health-related quality of life. Given the well-recognized HPV epidemic, these data provide support for further investigation of antivascular therapy in patients with other HPV-induced tumors, including vulvar, anal, penile, and oropharyngeal carcinomas.

Two additional agents that may have activity in advanced cervical cancer are pazopanib, an intra-cellular small-molecule tyrosine kinase in hibitor that targets VEGF receptor, and sorafenib, a multikinase inhibitor.[38] Data are lacking on drugs that inhibit angiogenesis through non– VEGF-dependent pathways (e.g., the Tie2–angiopoietin-2 pathway), as well as vascular disrupting agents (e.g., vadime zan). Finally, drugs targeting nonangiogenic signal-transduction pathways that are integral to tumor progression may be considered, including Wee1 checkpoint inhibitors and Notch γ-secretase inhibitors, the latter being an evolutionarily conserved cell-fate decision switch in cervical cancer.

There has been a large unmet medical need for active treatments for cervical cancer, which is a leading cause of death from cancer in developing countries. In the poorest regions, where rates are highest (sub-Saharan Africa, Latin America, and Southeast Asia, including India), many women are forced by socioeconomic and political circumstances to act as the sole provider for their young families. With their deaths, the effect on families can be devastating. The improvement in survival that is conferred by cisplatin–paclitaxel–bevacizumab treatment warrants cost-effectiveness studies because of the societal burden involved in making expensive therapies available to those in greatest need. However, the key to solving the global burden of cervical cancer continues to be the implementation of screening and vaccination programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013; 63:11–30. [PubMed: 23335087]

2. Tewari, KS.; Monk, BJ. Invasive cervical cancer.. In: DiSaia, PJ.; Creasman, WT., editors. Clinical gynecologic oncology. 8th ed.. Mosby; Philadelphia: 2012.
3. Monk BJ, Tewari KS, Koh WJ. Multi-modality therapy for locally advanced cervical carcinoma: state of the art and future directions. J Clin Oncol. 2007; 25:2952–65. [PubMed: 17617527]
4. Tewari KS. Expert panel: patients with metastatic/recurrent cervical cancer should be treated with cisplatin plus paclitaxel. Clin Ovarian Cancer. 2011; 4:90–3.
5. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2009; 27:4649–55. [PubMed: 19720909]
6. Tewari KS. A critical need for reappraisal of therapeutic options for women with metastatic and recurrent cervical carcinoma: commentary on Gynecologic Oncology Group protocol 204. Am J Hematol Oncol. 2010; 9:31–4.
7. Tewari KS, Monk BJ. The rationale for the use of non-platinum chemotherapy doublets for metastatic and recurrent cervical carcinoma. Clin Adv Hematol Oncol. 2010; 8:108–15. [PubMed: 20386532]
8. Tewari KS, Monk BJ. Gynecologic oncology group trials of chemotherapy for metastatic and recurrent cervical cancer. Curr Oncol Rep. 2005; 7:419–34. [PubMed: 16221379]
9. Bonomi P, Blessing JA, Stehman FB, DiSaia PJ, Walton L, Major FJ. Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol. 1985; 3:1079–85. [PubMed: 3894589]
10. Thigpen JT, Blessing JA, DiSaia PJ, Fowler WC Jr, Hatch KD. A randomized comparison of a rapid versus prolonged (24 hr) infusion of cisplatin in therapy of squamous cell carcinoma of the uterine cervix: a Gynecologic Oncology Group study. Gynecol Oncol. 1989; 32:198–202. [PubMed: 2910782]
11. McGuire WP III, Arseneau J, Blessing JA, et al. A randomized comparative trial of carboplatin and iproplatin in advanced squamous carcinoma of the uterine cervix: a Gynecologic Oncology Group study. J Clin Oncol. 1989; 7:1462–8. [PubMed: 2674333]
12. Omura GA, Blessing JA, Vaccarello L, et al. Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol. 1997; 15:165–71. [PubMed: 8996138]
13. Bloss JD, Blessing JA, Behrens BC, et al. Randomized trial of cisplatin and ifosfamide with or without bleomycin in squamous carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol. 2002; 20:1832–7. [PubMed: 11919241]
14. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol. 2004; 22:3113–9. [PubMed: 15284262]
15. Long HJ III, Bundy BN, Grendys EC Jr, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. J Clin Oncol. 2005; 23:4626–33. [PubMed: 15911865]
16. Moore DH, Tian C, Monk BJ, Long HJ, Omura GA, Bloss JD. Prognostic factors for response to cisplatin-based chemotherapy in advanced cervical carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2010; 116:44–9. [PubMed: 19853287]
17. Tewari KS, Monk BJ. Recent achievements and future developments in advanced and recurrent cervical cancer: trials of the Gynecologic Oncology Group. Semin Oncol. 2009; 36:170–80. [PubMed: 19332251]
18. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science. 1989; 246:1306–9. [PubMed: 2479986]
19. Monk BJ, Sill MW, Burger RA, Gray HJ, Buekers TE, Roman LD. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncol ogy Group study. J Clin Oncol. 2009; 27:1069–74. [PubMed: 19139430]
20. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov. 2004; 3:391–400. [PubMed: 15136787]

21. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92:205–16. [PubMed: 10655437]
22. Cella, DF. Manual for the Functional Assessment of Cancer Therapy (FACT) measurement system (version 4). Northwestern University, Center for Outcomes, Research and Education (CORE); Chicago: 1997.
23. Common Terminology Criteria for Adverse Events (CTCAE), v3.0. Cancer Therapy Evaluation Program; Bethesda, MD: 2006. (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_30)
24. Common Terminology Criteria for Adverse Events (CTCAE). v4.0. Cancer Therapy Evaluation Program; Bethesda, MD: 2011. (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40)
25. Tewari KS, Monk BJ. Beyond platinum for metastatic and recurrent carcinoma of the cervix. Onkologie. 2009; 32:552–4. [PubMed: 19816070]
26. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep. 1966; 50:163–70. [PubMed: 5910392]
27. Cox DR. Regression models and life-tables. J R Stat Soc [B]. 1972; 34:187–220.
28. Wieand S, Schroeder G, O'Fallon JR. Stopping when the experimental regimen does not appear to help. Stat Med. 1994; 13:1453–8. [PubMed: 7973224]
29. Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983; 70:659–63.
30. Diggle, P.; Liang, KY.; Zeger, SL. Analysis of longitudinal data. Clarendon Press; Oxford, United Kingdom: 1993.
31. Bahadori HR, Green MR, Catapano CV. Synergistic interaction between topotecan and microtubule-interfering agents. Cancer Chemother Pharmacol. 2001; 48:188–96. [PubMed: 11592339]
32. Tiersten AD, Selleck MJ, Hershman DL, et al. Phase II study of topotecan and paclitaxel for recurrent, persistent, or metastatic cervical carcinoma. Gynecol Oncol. 2004; 92:635–8. [PubMed: 14766258]
33. No JH, Jo H, Kim SH, et al. Expression of vascular endothelial growth factor and hypoxia inducible factor-1alpha in cervical neoplasia. Ann N Y Acad Sci. 2009; 1171:105–10. [PubMed: 19723043]
34. Tang X, Zhang Q, Nishitani J, Brown J, Shi S, Le AD. Overexpression of human papillomavirus type 16 oncoproteins enhances hypoxia-inducible factor 1 alpha protein accumulation and vascular endothelial growth factor expression in human cervical carcinoma cells. Clin Cancer Res. 2007; 13:2568–76. [PubMed: 17473185]
35. Tewari KS, Taylor JA, Liao SY, et al. Development and assessment of a general theory of cervical carcinogenesis utilizing a severe combined immunodeficiency murine-human xenograft model. Gynecol Oncol. 2000; 77:137–48. [PubMed: 10739703]
36. Clere N, Bermont L, Fauconnet S, et al. The human papillomavirus type 18 E6 oncoprotein induces vascular endothelial growth factor 121 (VEGF121) transcription from the promoter through a p53-independent mechanism. Exp Cell Res. 2007; 313:3239–50. [PubMed: 17678892]
37. Bodily JM, Mehta KP, Laimins LA. Human papillomavirus E7 enhances hypoxiainducible factor 1-mediated transcription by inhibiting binding of histone deacetylases. Cancer Res. 2011; 71:1187–95. [PubMed: 21148070]
38. Monk BJ, Mas Lopez L, Zarba JJ, et al. Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. J Clin Oncol. 2010; 28:3562–9. [PubMed: 20606083]

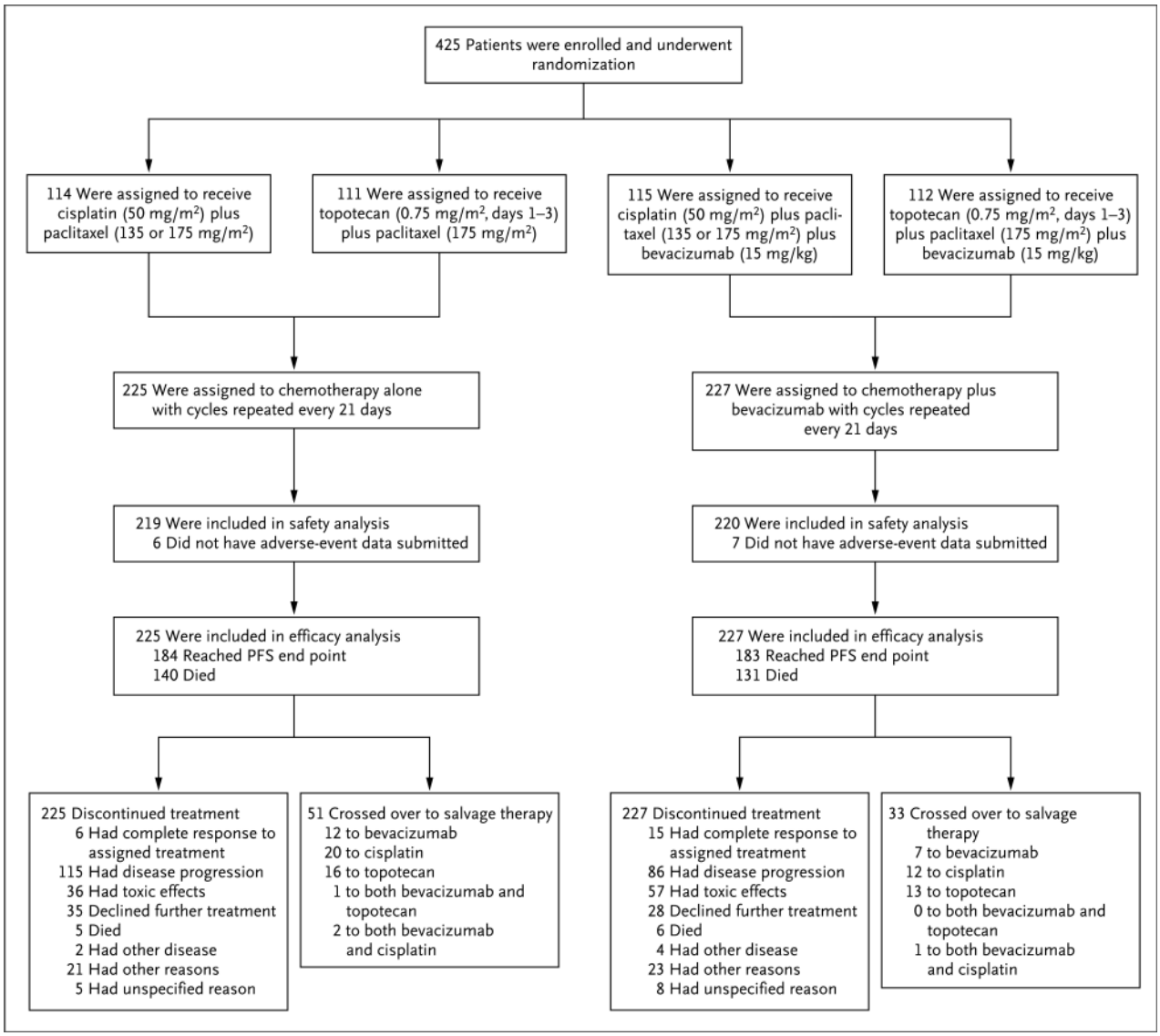

Figure 1. Enrollment, Randomization, and Follow-up of the Study Patients.

All 452 patients (225 in the chemotherapy-alone group and 227 in the chemotherapy-plus-bevacizumab group) who underwent randomization were included in the efficacy analysis. Because data on adverse events were not included for 6 patients in the chemotherapy-alone group, the safety analysis in this group included 219 patients. Because data on adverse events were not included for 7 patients in the chemotherapy-plus-bevacizumab group, the safety analysis in this group included 220 patients. A total of 15 patients randomly assigned to chemotherapy alone crossed over to salvage bevacizumab at the time of disease progression. PFS denotes progression-free survival.

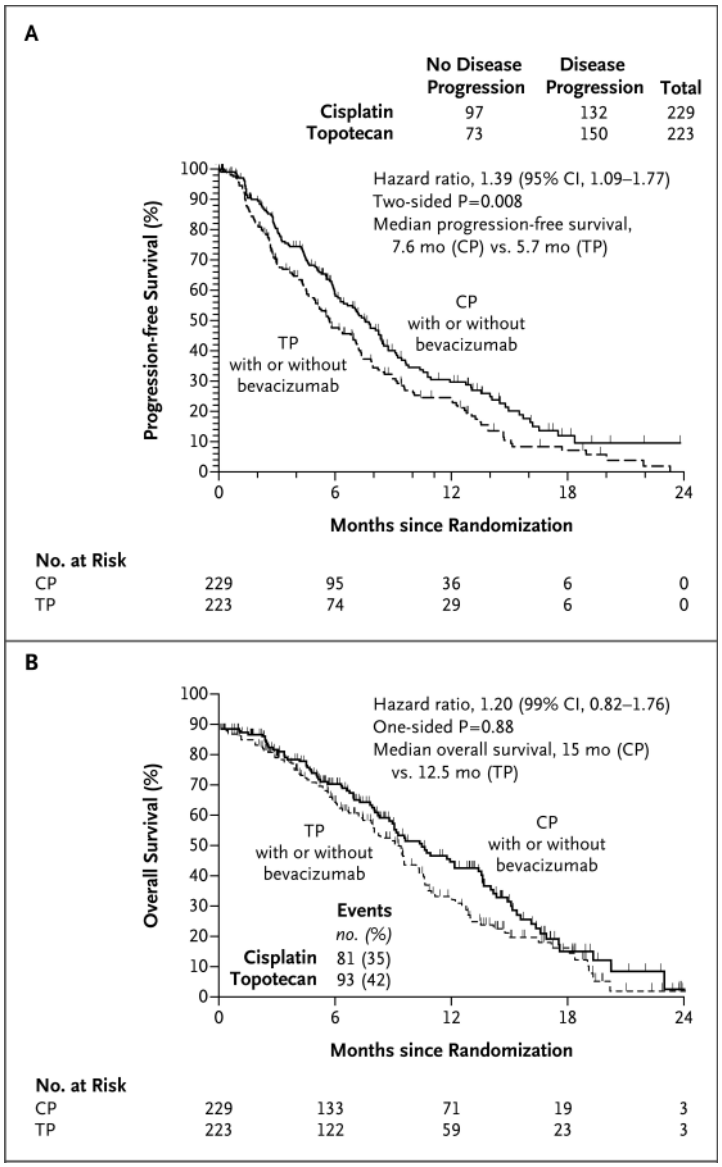

Figure 2. Progression-free and Overall Survival, According to the Chemotherapy Regimen.

Shown are progression-free survival (Panel A) and overall survival (Panel B) among patients assigned to cisplatin–paclitaxel (CP) chemotherapy with or without bevacizumab and those assigned to topotecan–paclitaxel (TP) chemotherapy with or without bevacizumab. An interim analysis showed that as compared with CP with or without bevacizumab, TP with or without bevacizumab was associated with a significantly higher risk of progression but did not significantly affect overall survival.

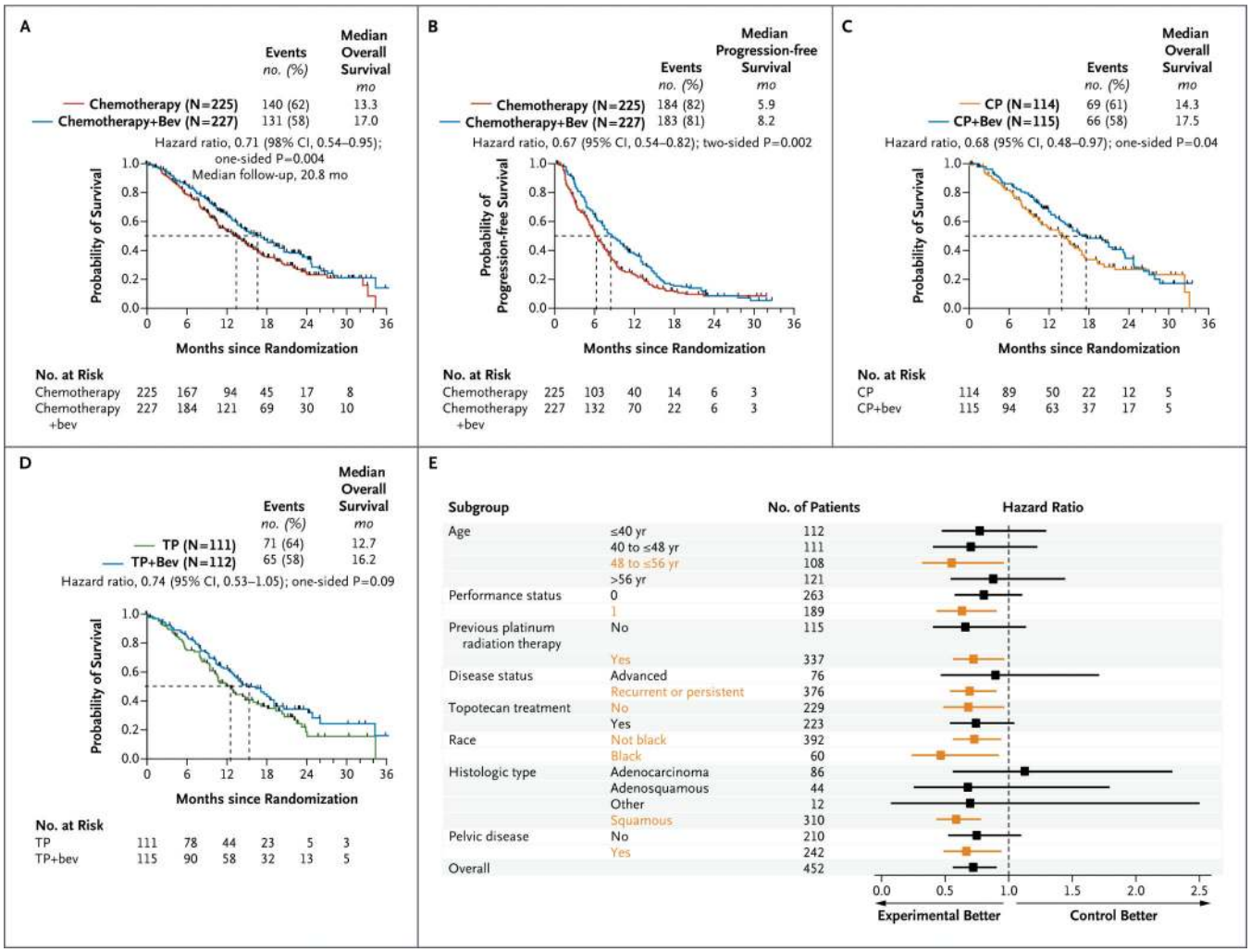

Figure 3. Effect of Incorporation of Bevacizumab on Survival.

Panel A shows overall survival and Panel B shows progression-free survival among patients who received either chemotherapy regimen plus bevacizumab or either chemotherapy regimen alone. Panel C shows overall survival among patients who received cisplatin–paclitaxel with or without bevacizumab, and Panel D shows overall survival among those who received topotecan–paclitaxel with or without bevacizumab. In Panel E, a forest plot shows the effect of chemotherapy with bevacizumab(experimental), as compared with chemotherapy with out bevacizumab (control), on overall survival, stratified according to multiple prognostic factors. A positive treatment benefit (orange) is indicated. The upper bound of the confidence interval for histologic type was truncated at 2.5. Its true upper bound, 7.07, resulted from a small sample. An interaction test was performed, and nothing was found to be significant. The factor with the smallest P value was histologic type (P = 0.07).

Table 1

Selected Adverse Events among the Study Patients, According to Treatment Group.*

Event	Chemotherapy Alone (N = 219)	Chemotherapy plus Bevacizumab (N = 220)	Odds Ratio (95% CI)	P Value
no. of patients (%)				
Gastrointestinal events, excluding fistulas (grade ≥2)	96 (44)	114 (52)	1.38 (0.93–2.04)	0.10
Fistula (grade ≥3)				
Gastrointestinal	0	7 (3)	NA (1.90–∞)	0.02
Genitourinary	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12
Total†	1 (<1)	13 (6)	13.69 (2.01–584.00)	0.002
Hypertension (grade ≥2)‡	4 (2)	54 (25)	17.50 (6.23–67.50)	<0.001
Proteinuria (grade ≥3)	0	4 (2)	NA (0.90–∞)	0.12
Pain (grade ≥2)	62 (28)	71 (32)	1.21 (0.79–1.85)	0.41
Neutropenia (grade ≥4)	57 (26)	78 (35)	1.56 (1.02–2.40)	0.04
Febrile neutropenia (grade ≥3)	12 (5)	12 (5)	1.00 (0.40–2.48)	1.00
Thromboembolism (grade ≥3)	3 (1)	18 (8)	6.42 (1.83–34.4)	0.001
CNS bleeding (grade ≥3)	0	0	NA	
Gastrointestinal bleeding (grade ≥3)§	1 (<1)	4 (2)	4.04 (0.39–200.00)	0.37
Genitourinary bleeding (grade ≥3)§	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12

*Adverse events were analyzed for any patient who received protocol-directed therapy and for whom adverse event information was submitted. CNS denotes central nervous system, and NA not applicable.

†Fistulas were mainly managed supportively; one patient underwent colostomy and another received nephrostomy tubes.

‡Hypertension of grade 2 or higher was defined as recurrent or continuous hypertension for a period of more than 24 hours or a symptomatic increase in blood pressure by more than 20 mm Hg diastolic or to more than 150/100 mm Hg if the blood pressure was previously within the normal range.

§Bleeding was managed primarily with supportive therapy and transfusions of packed red cells, most commonly in the outpatient setting.