ORIGINAL ARTICLE

Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

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ABSTRACT

BACKGROUND

Vascular endothelial growth factor is a key promoter of angiogenesis and disease progression in epithelial ovarian cancer. Bevacizumab, a humanized anti–vascular endothelial growth factor monoclonal antibody, has shown single-agent activity in women with recurrent tumors. Thus, we aimed to evaluate the addition of bevacizumab to standard front-line therapy.

METHODS

In our double-blind, placebo-controlled, phase 3 trial, we randomly assigned eligible patients with newly diagnosed stage III (incompletely resectable) or stage IV epithelial ovarian cancer who had undergone debulking surgery to receive one of three treatments. All three included chemotherapy consisting of intravenous paclitaxel at a dose of 175 mg per square meter of body-surface area, plus carboplatin at an area under the curve of 6, for cycles 1 through 6, plus a study treatment for cycles 2 through 22, each cycle of 3 weeks' duration. The control treatment was chemotherapy with placebo added in cycles 2 through 22; bevacizumab-initiation treatment was chemotherapy with bevacizumab (15 mg per kilogram of body weight) added in cycles 2 through 6 and placebo added in cycles 7 through 22. Bevacizumab-throughout treatment was chemotherapy with bevacizumab added in cycles 2 through 22. The primary end point was progression-free survival.

RESULTS

Overall, 1873 women were enrolled. The median progression-free survival was 10.3 months in the control group, 11.2 in the bevacizumab-initiation group, and 14.1 in the bevacizumab-throughout group. Relative to control treatment, the hazard ratio for progression or death was 0.908 (95% confidence interval [CI], 0.795 to 1.040; P=0.16) with bevacizumab initiation and 0.717 (95% CI, 0.625 to 0.824; P<0.001) with bevacizumab throughout. At the time of analysis, 76.3% of patients were alive, with no significant differences in overall survival among the three groups. The rate of hypertension requiring medical therapy was higher in the bevacizumab-initiation group (16.5%) and the bevacizumab-throughout group (22.9%) than in the control group (7.2%). Gastrointestinal-wall disruption requiring medical intervention occurred in 1.2%, 2.8%, and 2.6% of patients in the control group, the bevacizumab-initiation group, and the bevacizumab-throughout group, respectively.

CONCLUSIONS

The use of bevacizumab during and up to 10 months after carboplatin and paclitaxel chemotherapy prolongs the median progression-free survival by about 4 months in patients with advanced epithelial ovarian cancer. (Funded by the National Cancer Institute and Genentech; ClinicalTrials.gov number, NCT00262847.)

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*The member institutions of the Gynecologic Oncology Group that participated in this study are listed in the Supplementary Appendix, available at NEJM.org.

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Epithelial ovarian cancer and related cancers lead to 15,000 deaths in the United States annually, representing the fifth leading cause of death from cancer among women.[1] The poor prognosis is usually attributed to advanced stage at diagnosis and inadequate chemotherapy.

Vascular endothelial growth factor (VEGF) and angiogenesis are important promoters of ovarian-cancer progression.[2-6] Both correlate directly with the extent of disease and inversely with progression-free survival[7-9] and overall survival,[8,10-13] often independently of known prognostic factors.[7-10,12,13] Bevacizumab, a humanized VEGF-neutralizing monoclonal antibody, inhibits tumor angiogenesis[14] and has shown single-agent activity in phase 2 epithelial ovarian cancer trials.[15,16] We investigated the integration of bevacizumab into front-line ovarian cancer therapy.

Methods

Patients

Eligibility criteria (see the Supplementary Appendix, available with the full text of this article at NEJM.org) included previously untreated, incompletely resectable stage III or any stage IV epithelial ovarian, primary peritoneal, or fallopian-tube cancer histologically confirmed by the Gynecologic Oncology Group (GOG) Pathology Committee after standard abdominal surgery with maximal debulking effort within 12 weeks before study entry; a GOG performance status score (see the Supplementary Appendix) of 0 (fully active) to 2 (ambulatory and capable of self-care but unable to work; up and about more than 50% of waking hours); and no history of clinically significant vascular events or evidence of intestinal obstruction. Owing to competing trials, patients with stage III disease and no residual lesions greater than 1 cm in maximal diameter were initially excluded, but after a protocol modification they were permitted. All patients provided written informed consent before enrollment.

Study Design

The study (number GOG-0218) was a double-blind, placebo-controlled phase 3 trial (see the Supplementary Appendix). The protocol is available at NEJM.org. The authors wrote the manuscript and take responsibility for the accuracy and completeness of the reported data and for the fidelity of the report to the protocol.

Each of the three study regimens comprised 22 3-week cycles with intravenous infusions on day 1, with the first 6 cycles consisting of standard chemotherapy with carboplatin at an area under the curve of 6 and paclitaxel at a dose of 175 mg per square meter of body-surface area. Control treatment was chemotherapy with placebo added in cycles 2 through 22; bevacizumab-initiation treatment was chemotherapy with bevacizumab (15 mg per kilogram of body weight) added in cycles 2 through 6 and placebo added in cycles 7 through 22. Bevacizumab-throughout treatment was chemotherapy with bevacizumab added in cycles 2 through 22. Bevacizumab or placebo was initiated at cycle 2, rather than cycle 1, to reduce the risk of wound-healing complications. Treatment was discontinued at the onset of disease progression, unacceptable toxic effects, completion of all 22 cycles, or withdrawal — whichever came first.

Disease was assessed before cycle 1 by means of computed tomography or magnetic resonance imaging of at least the abdomen and pelvis, measurement of the serum cancer antigen 125 (CA-125) level,[17] and physical examination. In patients without progression, imaging was repeated after treatment cycles 3, 6, 10, 14, 18, and 22. Serum CA-125 levels were measured and physical examinations were performed at the beginning of each cycle for cycles 1 through 6 (chemotherapy) and at the beginning of alternate cycles for cycles 7 through 22 (extended therapy). After completing study treatment, disease assessments were repeated every 3 months for 2 years, then every 6 months for 3 years, and then annually. The quality of life was compared among the three groups with the use of the Trial Outcome Index of the Functional Assessment of Cancer Therapy–Ovary (FACT-O TOI) survey.[18] The summary score based on the survey, with a possible total of 112 points and higher scores indicating better quality of life, encompasses aspects of quality of life in patients with advanced ovarian cancer (e.g., pain, fatigue, abdominal symptoms, and functional status). Questionnaires were completed before cycles 1, 4, 7, 13, and 22, as well as 6 months after completing the study therapy. Disease and quality-of-life evaluations were performed at these time points even if patients discontinued treatment (except if they discontinued because of disease progression, in which case disease evaluations were omitted).

Safety was monitored during each cycle. Ad-

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ministration of myeloid growth factor was permitted only to manage febrile neutropenia or grade 4 neutropenia (absolute neutrophil count, <500 per cubic millimeter) persisting for 7 days or more or as subsequent prophylaxis. In patients with limiting peripheral neuropathy or hypersensitivity, paclitaxel was replaced with docetaxel (75 mg per square meter) (see the Supplementary Appendix). The bevacizumab (and placebo) dose was modified only in patients whose weight changed by more than 10% but 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 >90 mm Hg), proteinuria (urine protein-to-creatinine ratio ≥3.5), wound or bowel-wall disruption (of any grade, during cycle 2 or later), reversible posterior leukoencephalopathy syndrome, arterial thrombosis (grade ≥3 at any time or grade 2 during cycle 2 or later), and venous thrombosis, coagulopathy, intestinal obstruction, or hypersensitivity of grade 3 or greater (see the Supplementary Appendix).

STATISTICAL ANALYSIS

The statistical analysis plan is available at NEJM.org. Patients were stratified on the basis of GOG performance-status score and cancer stage and debulking status (stage III cancer and maximal residual lesion diameter ≤1 cm vs. stage III cancer and maximal residual lesion diameter >1 cm vs. stage IV cancer) before being randomly assigned to a treatment group according to a minimization procedure.[19]

The primary end point was initially specified as overall survival but was changed to progression-free survival during the trial (see the Discussion section). Thereafter, treatment assignments could be revealed to the study investigators and patients if documented progression occurred. Progression-free survival and overall survival were calculated from the date of enrollment. Progression-free survival was considered to have ended at the time of cancer progression as shown on radiography, according to the Response Evaluation Criteria in Solid Tumors criteria (see the Supplementary Appendix)[20]; an increase in the CA-125 level according to Gynecologic Cancer InterGroup criteria[21]; global deterioration of health; or death from any cause. Progression defined solely on the basis of increased CA-125 level was permitted only if the patient had completed chemotherapy. If patients remained free of progression at their last follow-up visit, data on duration of progression-free survival were censored at the time of the last radiographic assessment.

Differences in progression-free survival among the three groups were assessed by means of the log-rank test.[22] A sample size of 1800 was estimated to provide 90% statistical power to detect a 23% reduction in the hazard for progression with either of the two bevacizumab-containing regimens versus the control regimen while limiting the overall one-sided type I error for both comparisons to 2.5%. The final analysis was planned to be conducted after at least 375 patients in the control group died or had disease progression. Relative hazard ratios were estimated with the use of a proportional-hazards model.[23] The progression-free survival and overall survival analyses included all enrolled patients. All reported P values are two-sided.

Differences in FACT-O TOI scores among the three groups were assessed by means of a linear mixed model with adjustment for baseline score and age. Assessment time points were treated as categorical. Hypotheses were tested at a 1.67% significance level to account for multiple comparisons.

Adverse events, graded with the use of National Cancer Institute Common Terminology Criteria for adverse events (version 3),[24] were reported until 30 days after the last study treatment had been administered and were summarized for patients who received at least one cycle of bevacizumab or placebo. Differences among the groups in the severity of adverse events were examined by means of Fisher's exact test.[25]

RESULTS

PATIENTS

Between October 2005 and June 2009, 1873 women were enrolled from 336 institutions in the United States, Canada, South Korea, and Japan (Fig. 1). By the time eligibility was broadened in July 2007, a total of 467 patients had enrolled; 1299 had enrolled by October 2008, when the primary end point was changed to progression-free survival. A complete data sweep was initiated on January 2, 2010, and the database was locked on February 5, 2010.

Factors that could influence treatment outcome were evenly distributed across treatment groups (Table 1). Over 80% of patients were non-Hispanic white, over 80% had serous adenocarcinomas,

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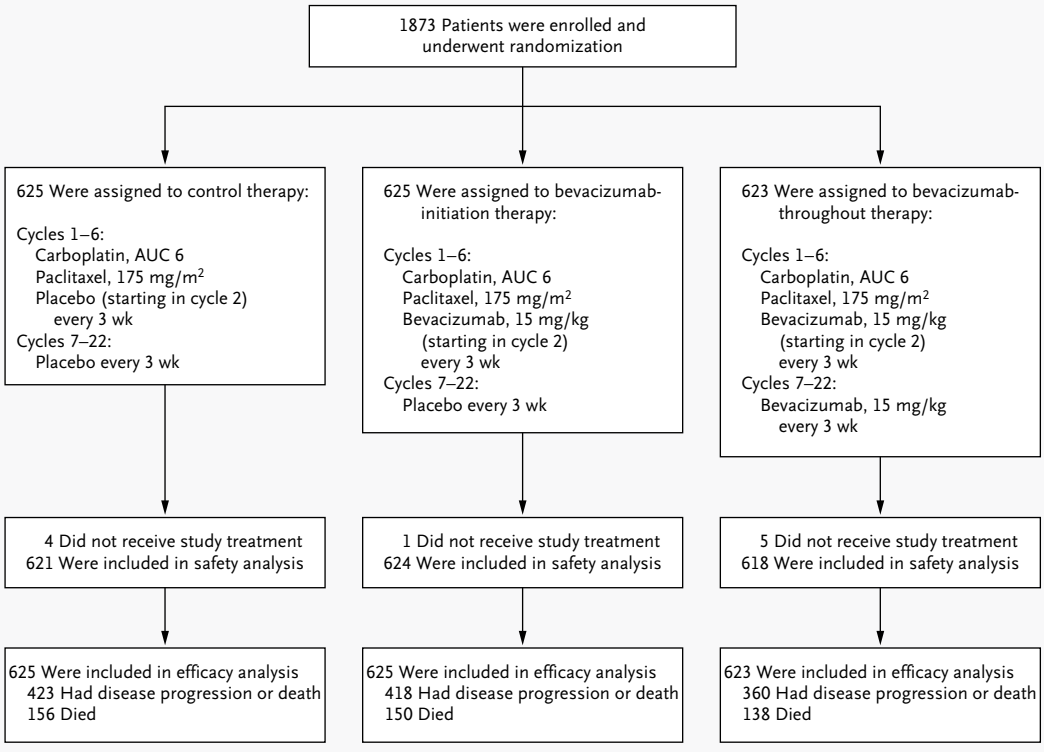

Figure 1. Enrollment, Randomization, and Follow-up of the Study Patients.

After pathological review and review of the case-report forms, 29 enrolled patients were found to have tumor characteristics that would have rendered them ineligible: 13 had a stage of cancer according to the International Federation of Gynecology and Obstetrics (FIGO) staging system that did not meet the eligibility criteria, 5 had an inadequate specimen for central review, 3 had borderline tumors (low malignant potential), 7 had histologic characteristics that made them ineligible, and 1 had an invalid primary-tumor site. Data on these patients were analyzed as if they had been eligible. AUC denotes area under the curve.

and the majority of cancers were tumor grade 3. The cohort had a relatively poor prognosis: 40% had stage III cancer with maximal residual lesion diameter greater than 1 cm and 26% had stage IV disease.

Nineteen percent of patients overall (16%, 17%, and 24% in the control group, bevacizumab-initiation group, and the bevacizumab-throughout group, respectively) completed the planned treatment, and 15% overall were still receiving treatment (in the extended-therapy phase) at the time of the database lock (see the Supplementary Appendix). Sixty-six percent of the study population discontinued the study treatment prematurely; the most common reason was disease progression (affecting 48% of patients in the control group, 42% in the bevacizumab-initiation group, and 26% in the bevacizumab-throughout group). Treatment was discontinued owing to adverse events in a higher percentage of patients in the bevacizumab-initiation group (15%) and the bevacizumab-throughout group (17%) than in the control group (12%). Overall, 76% of adverse events leading to treatment discontinuation occurred during the chemotherapy phase.

EFFICACY

At the time of the primary analysis, 76.3% of patients were alive, with a median of 17.4 months of follow-up. The median progression-free survival was 10.3, 11.2, and 14.1 months in the control group, the bevacizumab-initiation group, and the bevacizumab-throughout group, respectively (Fig. 2A). As compared with the control group, the hazard of progression or death was lower (albeit not significantly) in the bevacizumab-initiation group (hazard ratio, 0.908; 95% confidence interval [CI], 0.795 to 1.040; P=0.16) and signifi-

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Table 1. Baseline Characteristics of the Patients, According to Treatment Group.*

Characteristic	Bevacizumab Initiation (N=625)	Bevacizumab Throughout (N=623)	Control (N=625)
Age — yr			
Median	60	60	60
Range	24–88	22–89	25–86
Race or ethnic group — no. (%)†			
Non-Hispanic white	519 (83.0)	521 (83.6)	526 (84.2)
Asian	37 (5.9)	39 (6.3)	41 (6.6)
Non-Hispanic black	28 (4.5)	27 (4.3)	25 (4.0)
Hispanic	28 (4.5)	25 (4.0)	21 (3.4)
Other or unspecified	13 (2.1)	11 (1.8)	12 (1.9)
GOG performance status — no. (%)‡			
0	315 (50.4)	305 (49.0)	311 (49.8)
1	270 (43.2)	267 (42.9)	272 (43.5)
2	40 (6.4)	51 (8.2)	42 (6.7)
Stage/debulking status — no. (%)			
III (macroscopic, ≤1 cm)	205 (32.8)	216 (34.7)	218 (34.9)
III (>1 cm)	256 (41.0)	242 (38.8)	254 (40.6)
IV	164 (26.2)	165 (26.5)	153 (24.5)
Histologic type — no. (%)§			
Serous adenocarcinoma	519 (83.0)	524 (84.1)	541 (86.6)
Endometrioid	14 (2.2)	24 (3.9)	21 (3.4)
Clear cell	23 (3.7)	20 (3.2)	12 (1.9)
Mucinous	5 (0.8)	8 (1.3)	6 (1.0)
Other or not specified	64 (10.2)	47 (7.5)	45 (7.2)
Tumor grade — no. (%)§			
3	465 (74.4)	460 (73.8)	445 (71.2)
2	86 (13.8)	97 (15.6)	102 (16.3)
1	28 (4.5)	18 (2.9)	36 (5.8)
Not graded	46 (7.4)	48 (7.7)	42 (6.7)

* Percentages may not sum to 100 because of rounding.
† Race or ethnic group was self-reported.
‡ A Gynecologic Oncology Group (GOG) performance status score of 0 indicates that the patient is fully active, 1 that the patient is restricted in physically strenuous activities but ambulatory, and 2 that the patient is ambulatory and capable of self-care but unable to work.
§ Histologic type and tumor grade were obtained from the central GOG Pathology Committee review updated in September 2010. All clear-cell tumors were classified as grade 3.

cantly lower in the bevacizumab-throughout group (hazard ratio, 0.717; 95% CI, 0.625 to 0.824; P<0.001). The maximal separation of the progression-free survival curves for the bevacizumab-throughout group and the control group occurred at 15 months, with convergence approximately 9 months later. In an analysis of progression-free survival in which data for patients with increased CA-125 levels were censored, as required by regulatory agencies, the median progression-free survival was 12.0 months in the control group but 18.0 months in the bevacizumab-throughout group (hazard ratio, 0.645; 95% CI, 0.551 to 0.756; P<0.001) (see the Supplementary Appendix). The estimated treatment effect on progression-free survival with bevacizumab throughout as compared with control treatment was consistent across various prognostic factors (Fig. 2C).

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The median overall survival was 39.3, 38.7, and 39.7 months for the control group, the bevacizumab-initiation group, and the bevacizumab-throughout group, respectively (Fig. 3). As compared with the control group, the hazard of death was 1.036 (95% CI, 0.827 to 1.297; P=0.76) in the bevacizumab-initiation group and 0.915 (95% CI, 0.727 to 1.152; P=0.45) in the bevacizumab-throughout group.

Results of updated analyses of progression-free survival (Fig. 2B) and overall survival (Fig. 3B), performed on the data as of August 26, 2011, after 47% of the patients had died, were consistent with those from the original analyses.

Figure 2 (facing page). Primary and Subgroup Analyses of Progression-free Survival, According to Treatment Group.

Panel A shows the results of primary analysis of progression-free survival for all 1873 patients randomly assigned to receive chemotherapy with carboplatin and paclitaxel (CP) plus placebo followed by placebo alone (the control group), CP plus bevacizumab (bev) followed by placebo (the bevacizumab-initiation group), or CP plus bevacizumab followed by bevacizumab (the bevacizumab-throughout group). There was a significant, time-dependent decrease in the hazard of progression in the bevacizumab-throughout group as compared with the control group (hazard ratio, 0.717; 95% confidence interval [CI], 0.625 to 0.824; P<0.001). Panel B shows the results of an updated analysis of data on progression-free survival as of August 26, 2011. The hazard of progression remained significantly decreased with bevacizumab-throughout versus control therapy (hazard ratio, 0.770; 95% CI, 0.681 to 0.870). Panel C shows the effect of treatment with bevacizumab (vs. control) on progression-free survival, stratified according to multiple prognostic factors. The effect was significant and consistent across all strata for bevacizumab throughout (vs. control). GOG denotes Gynecologic Oncology Group.

QUALITY OF LIFE

Valid quality-of-life surveys were available for 93.2%, 88.3%, 85.8%, 81.1%, 75.7%, and 74.1% of patients alive before cycles 1, 4, 7, 13, and 22 and 6 months after completing the study therapy, respectively. There were no significant differences across the three treatment groups. The mean FACT-O TOI scores exceeded 65 at each time point and generally increased over the duration of the study, reaching more than 75 by 6 months after the completion of chemotherapy. During the chemotherapy phase, the mean FACT-O TOI scores were slightly lower in the bevacizumab-initiation group and the bevacizumab-throughout group than in the control group, especially before cycle 4 (with a reduction of 2.7 points [98.3% CI, 0.88 to 4.57; P<0.001] and 3.0 points [98.3% CI, 1.13 to 4.78; P<0.001], respectively). No significant differences were found in the mean FACT-O TOI scores between the control group and the bevacizumab-throughout group at any of the three time points after completion of chemotherapy.

SAFETY

Table 2 shows the frequency of adverse events potentially associated with bevacizumab (on the basis of prior trials). Hypertension of grade 2 or greater was significantly (P<0.001) more common with bevacizumab than placebo but led to discontinuation of bevacizumab in only 15 of the 608 patients (2.4%) in the bevacizumab-throughout group. There were no significant differences among the three groups in the rates of other adverse events, including gastrointestinal perforation or fistula, proteinuria of grade 3 or greater, neutropenia of grade 4 or greater or febrile neutropenia, venous or arterial thrombosis, and wound disruption. Other adverse events, such as clinically relevant bleeding or central nervous system complications, were rare. Fatal adverse events were reported in 6 of 601 patients (1.0%) in the control group, in 10 of 607 patients (1.6%) in the bevacizumab-initiation group, and in 14 of 608 patients (2.3%) in the bevacizumab-throughout group.

Most adverse events were reported during the chemotherapy phase rather than the extended-therapy phase (see the Supplementary Appendix). For example, in each of the three groups, all but one gastrointestinal perforation or fistula occurred during receipt of chemotherapy. Exceptions were hypertension, proteinuria, and pain, which were more commonly reported during the extended-therapy phase than the chemotherapy phase among patients in the bevacizumab-throughout group.

DISCUSSION

This study showed a significant improvement in progression-free survival (i.e., an increase in median progression-free survival by 4 months) with bevacizumab plus chemotherapy (with carboplatin and paclitaxel) followed by extended bevacizumab therapy, as compared with chemotherapy alone, for advanced ovarian cancer. The effect was seen consistently across prognostic subgroups.

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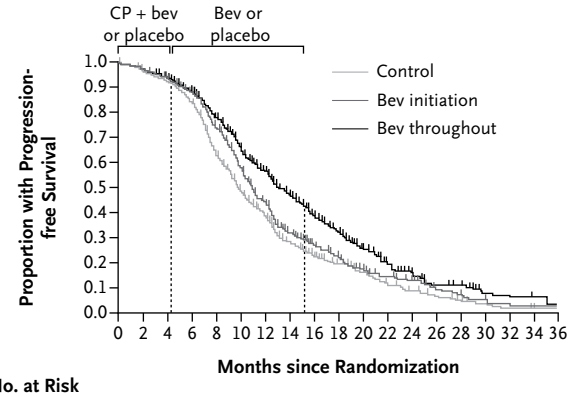
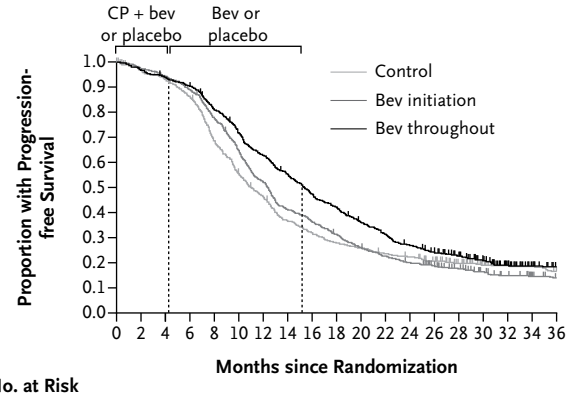
A Primary Analysis



No. at Risk				
Control	625	199	33	8
Bev initiation	625	219	29	6
Bev throughout	623	254	38	8

B Analysis as of August 26, 2011



No. at Risk							
Control	625	535	283	169	133	78	49
Bev initiation	625	552	319	190	121	67	40
Bev throughout	623	559	386	256	162	97	56

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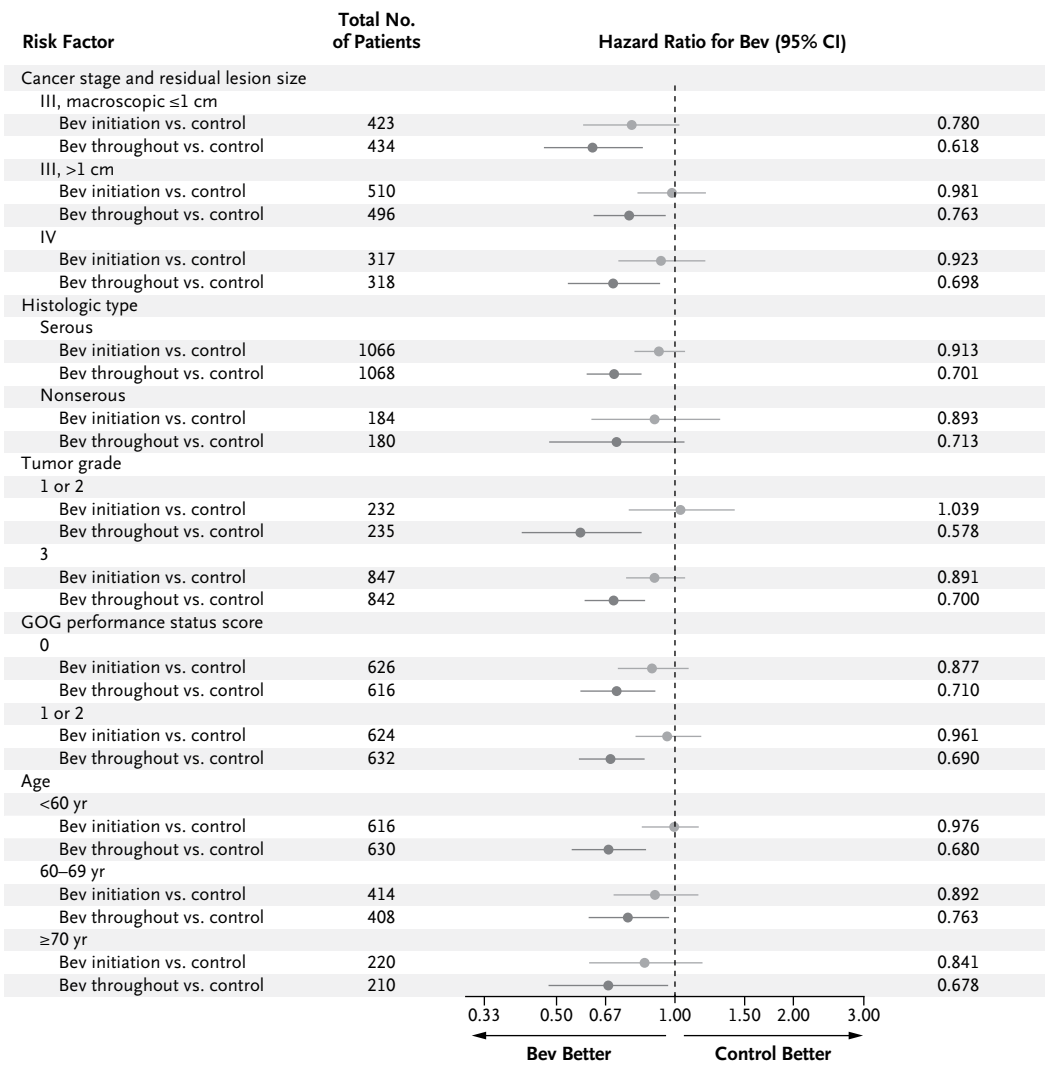

Risk Factor	Total No. of Patients	Hazard Ratio for Bev (95% CI)
Cancer stage and residual lesion size		
III, macroscopic ≤1 cm		
Bev initiation vs. control	423	0.780
Bev throughout vs. control	434	0.618
III, >1 cm		
Bev initiation vs. control	510	0.981
Bev throughout vs. control	496	0.763
IV		
Bev initiation vs. control	317	0.923
Bev throughout vs. control	318	0.698
Histologic type		
Serous		
Bev initiation vs. control	1066	0.913
Bev throughout vs. control	1068	0.701
Nonserous		
Bev initiation vs. control	184	0.893
Bev throughout vs. control	180	0.713
Tumor grade		
1 or 2		
Bev initiation vs. control	232	1.039
Bev throughout vs. control	235	0.578
3		
Bev initiation vs. control	847	0.891
Bev throughout vs. control	842	0.700
GOG performance status score		
0		
Bev initiation vs. control	626	0.877
Bev throughout vs. control	616	0.710
1 or 2		
Bev initiation vs. control	624	0.961
Bev throughout vs. control	632	0.690
Age		
<60 yr		
Bev initiation vs. control	616	0.976
Bev throughout vs. control	630	0.680
60–69 yr		
Bev initiation vs. control	414	0.892
Bev throughout vs. control	408	0.763
≥70 yr		
Bev initiation vs. control	220	0.841
Bev throughout vs. control	210	0.678

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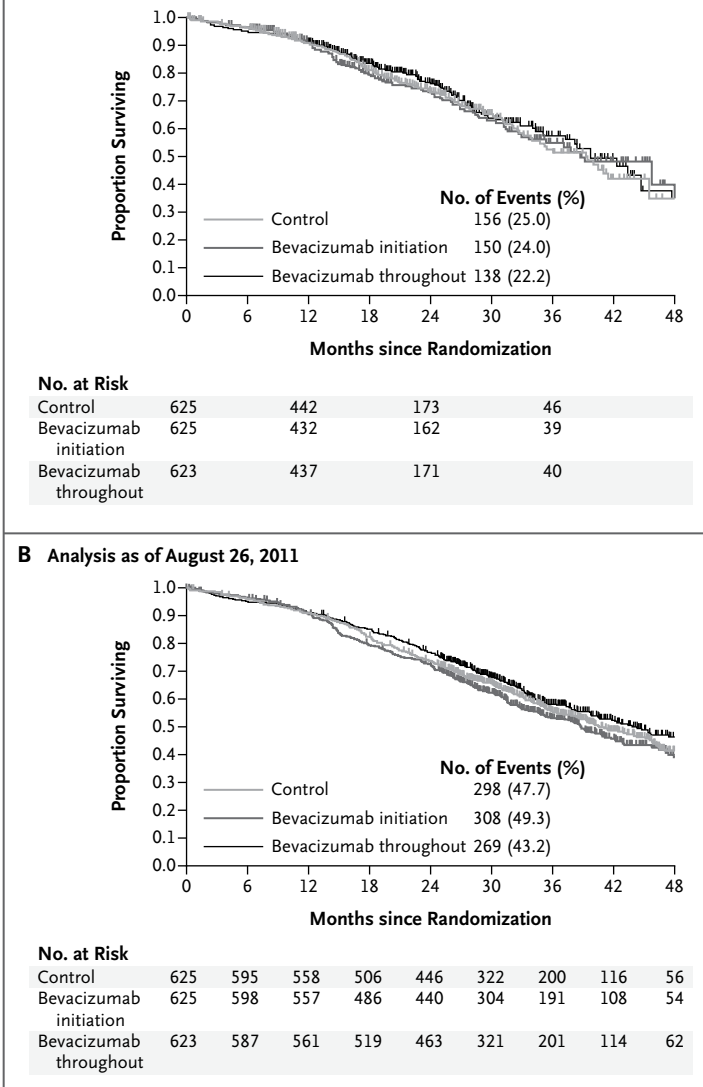

Figure 3. Analyses of Overall Survival, According to Treatment Group.

Panel A shows the results of the overall-survival analysis performed at the time of the primary analysis of progression-free survival, when 76.3% of patients were alive. As compared with patients receiving control therapy — chemotherapy with carboplatin and paclitaxel plus placebo followed by placebo — the hazard of death was 1.036 (95% confidence interval [CI], 0.827 to 1.29; P=0.76) among patients receiving carboplatin and paclitaxel plus bevacizumab followed by placebo (the bevacizumab-initiation group) and 0.915 (95% CI, 0.727 to 1.15; P=0.45) among patients receiving carboplatin and paclitaxel plus bevacizumab followed by bevacizumab (the bevacizumab-throughout group). Panel B shows the results of an updated analysis of data on overall survival as of August 26, 2011. At this time point, as compared with the control group, the hazard of death was 1.078 (95% CI, 0.919 to 1.270) in the bevacizumab-initiation group and 0.885 (95% CI, 0.750 to 1.040) in the bevacizumab-throughout group.

This finding supports results from earlier laboratory and epidemiologic studies, indicating that VEGF promotes progression in ovarian cancer[2-13] and that VEGF blockade inhibits tumor growth, metastasis, and malignant ascites formation.[2-5]

The 28% reduction in the risk of progression with bevacizumab throughout as compared with placebo is clinically important. Bevacizumab-related toxic effects after chemotherapy were similar to those seen in other tumor types, with no corresponding reduction in the quality of life. Since detection methods for ovarian cancer are highly sensitive, affected women tend to be asymptomatic at the time of initial disease progression. Therefore, we could not determine whether the delay in tumor progression per se delayed physical or psychological symptoms associated with disease or subsequent therapy. No significant improvement in overall survival was shown; however, the potential to detect a difference in survival is likely to be limited by lack of control for multiple subsequent regimens, including crossover to bevacizumab or other anti-VEGF agents.

Study therapy was discontinued because of adverse events in 17% of patients in the bevacizumab-throughout group versus 12% in the control group. The 5% difference between the groups may be overestimated, since more patients in the control group than in the bevacizumab-throughout group discontinued study treatment because of disease progression, after which adverse event reporting ended. Rates of gastrointestinal perforation and fistula in the two bevacizumab groups were almost twice those in the control group but were still less than 3%, consistent with rates seen in metastatic nongynecologic tumors. This is an important finding, given previous concerns about an excessive risk of gastrointestinal perforation in patients with recurrent ovarian cancer.[26] As expected, hypertension of grade 2 or higher was significantly more common with bevacizumab than without it. Although the risk of hypertension appeared to be cumulative, it was controlled with the use of medical therapy, with few patients discontinuing bevacizumab. The risk of proteinuria of grade 3 or higher also appeared to be cumulative, but proteinuria developed in less than 2% of patients in the bevacizumab-throughout group. In contrast to a

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Table 2. Selected Adverse Events among the Study Patients, According to Treatment Group.*

Event	Bevacizumab Initiation (N=607)	Bevacizumab Throughout (N=608)	Control (N=601)
		number of patients (percent)	
Gastrointestinal events (grade ≥2)†	17 (2.8)	16 (2.6)	7 (1.2)
Hypertension (grade ≥2)‡	100 (16.5)§	139 (22.9)§	43 (7.2)
Proteinuria (grade ≥3)	4 (0.7)	10 (1.6)	4 (0.7)
Pain (grade ≥2)	252 (41.5)	286 (47.0)	250 (41.6)
Neutropenia (grade ≥4)	384 (63.3)	385 (63.3)	347 (57.7)
Febrile neutropenia	30 (4.9)	26 (4.3)	21 (3.5)
Venous thromboembolism	32 (5.3)	41 (6.7)	35 (5.8)
Arterial thromboembolism	4 (0.7)	4 (0.7)	5 (0.8)
Wound disruption	22 (3.6)	18 (3.0)	17 (2.8)
CNS bleeding	0	2 (0.3)	0
Non-CNS bleeding (grade ≥3)	8 (1.3)	13 (2.1)	5 (0.8)
Reversible posterior leukoencephalopathy syndrome	1 (0.2)	1 (0.2)	0

* Adverse events were those with onset between cycle 2 and 30 days after the date of the last treatment. CNS denotes central nervous system.
† Gastrointestinal events of grade 2 or greater were gastrointestinal-wall disruption: perforation, fistula, necrosis, or anastomotic leak.
‡ Hypertension of grade 2 or greater consisted of recurrent or continuous hypertension for a period of more than 24 hours or symptomatic increase in blood pressure by more than 20 mm Hg (diastolic) or to over 150/100 mm Hg if the blood pressure was previously within the normal range.
§ $P<0.05$ for the comparison with the control group.

pooled analysis of phase 3 trials of nongynecologic cancers,[27] we observed no significant increase in the incidence of arterial thrombotic events with bevacizumab. Slightly higher, although not significantly higher, rates of grade 4 or 5 neutropenia and febrile neutropenia were seen in the two bevacizumab groups than in the control group.

The lack of a significant difference in progression-free survival between the control group and the bevacizumab-initiation group implies that bevacizumab must be continued beyond chemotherapy to delay disease progression. The rationale for combining cytotoxic and anti-VEGF therapy arose from preclinical studies showing a transient reduction in tumor microvascular permeability and interstitial pressure,[28,29] with a theoretical increase in tumor perfusion, and therefore enhanced chemosensitivity.[30,31] It is impossible to determine whether such a mechanism operated in this study, since a regimen of carboplatin and paclitaxel plus placebo followed by bevacizumab was not evaluated. Therefore, we cannot rule out the possibility that bevacizumab exposure during the chemotherapy phase of the bevacizumab-throughout group contributed to the significant improvement in progression-free survival. Although bevacizumab use resulted in additional toxic effects, it was not associated with a decline in quality-of-life scores,[32] and after chemotherapy completion, no significant differences in quality-of-life scores were observed across the three treatment groups. Trials of other antiangiogenic agents, with pure maintenance designs, are ongoing.

For the bevacizumab-throughout group, the maximal treatment time (approximately 15 months) was selected to exceed the median expected progression-free survival for the population yet to ensure study feasibility. Although the "tail ends" of the progression-free survival curves may be relatively unreliable for patients in the bevacizumab-throughout group and the control

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group, with less than 3% of patients at risk for progression, a convergence of the curves was observed nonetheless. Convergence of the progression-free survival curves was also observed in an independent, positive, front-line, open-label, phase 3 ovarian cancer trial of the International Collaborative Ovarian Neoplasm (ICON) group known as ICON7 (ClinicalTrials.gov number, NCT00483782),[33] in which bevacizumab use was limited to 12 months. In our bevacizumab-throughout group and the ICON7 bevacizumab group, 24% and 62% of patients, respectively, completed all study therapy without disease progression. In our bevacizumab-throughout group, an additional 19% of patients were still receiving bevacizumab at the time of the database lock. In contrast to our findings, progression-free survival curves did not converge in the placebo-controlled phase 3 Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease (OCEANS, NCT00434642).[34] OCEANS showed a hazard ratio for progression-free survival of 0.484 favoring chemotherapy with bevacizumab followed by continued bevacizumab over chemotherapy with placebo followed by placebo. Unlike the front-line trials, in OCEANS, bevacizumab was continued until disease progression. Though cross-trial comparisons have clear caveats, these results suggest that the magnitude of benefit may correlate directly with treatment duration. This hypothesis is consistent with results of preclinical studies in which anti-VEGF therapy delayed tumor growth and extended survival in a variety of established tumor models and prevented regrowth of a subgroup of residual tumors after cytotoxic therapy, whereas discontinuation of anti-VEGF therapy resulted in regrowth.[35] This is not unexpected, since angiogenesis is a host-related process that can be inhibited but not eradicated.

The bevacizumab regimen of 15 mg per kilogram every 3 weeks in this study was based on the regimen approved in combination with carboplatin and paclitaxel for advanced non–small-cell lung cancer[36] and single-agent activity shown in two phase 2 trials in ovarian cancer.[15,16] OCEANS used the same dose and schedule.[34] ICON7 used a bevacizumab dose of 7.5 mg per kilogram,[33] albeit with a smaller magnitude of benefit in a broader patient population, without obvious differences in adverse events from those in our study population. Together, these independent phase 3 trials of ovarian cancer show a benefit of bevacizumab in the dose range of 7.5 to 15 mg per kilogram.

A major limitation of this study was the change of the primary end point from overall survival to progression-free survival. This change was made because maintaining the blinding of the treatment assignments after disease progression, which was required to protect the integrity of the data on overall survival, was contested by numerous investigators and patients and therefore was deemed infeasible. A primary end point of progression-free survival is supported by the Gynecologic Cancer Intergroup,[37] which noted that in trials assessing front-line therapy for advanced ovarian cancer, including those involving maintenance therapy, progression-free survival is most often the preferred primary end point, because of the confounding effect of post-recurrence or post-progression therapy on overall survival.

When considering the balance of clinical benefit for progression-free survival, quality-of-life preservation, and tolerability, our study shows that bevacizumab plus carboplatin and paclitaxel, followed by bevacizumab, could be considered a front-line treatment option for patients with advanced ovarian cancer. Further investigation is needed to optimize duration and timing of treatment, assess integration into or use after other standard front-line strategies (e.g., neoadjuvant or intraperitoneal chemotherapy), examine cost-effectiveness, and, perhaps most important, identify potential tumor or host biologic factors predictive of efficacy and adverse events with the ultimate goal of decreasing morbidity and mortality from this disease.

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