rapid communication

Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer

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abstract

PURPOSE We report the final, protocol-specified analysis of overall survival (OS) in GOG-0218, a phase III, randomized trial of bevacizumab in women with newly diagnosed ovarian, fallopian tube, or primary peritoneal carcinoma.

METHODS A total of 1,873 women with incompletely resected stage III to IV disease were randomly assigned 1:1:1 to six 21-day cycles of intravenous carboplatin (area under the concentration *v* time curve 6) and paclitaxel (175 mg/m^2) versus chemotherapy plus concurrent bevacizumab (15 mg/kg, cycles 2 to 6) versus chemotherapy plus concurrent and maintenance bevacizumab (cycles 2 to 22). Inclusion criteria included a Gynecologic Oncology Group performance status of 0 to 2 and no history of clinically significant vascular events or evidence of intestinal obstruction. OS was analyzed in the intention-to-treat population. A total of 1,195 serum and/or tumor specimens were sequenced for *BRCA1/2* and damaging mutations in homologous recombination repair (HRR) genes. Intratumoral microvessel density was studied using CD31 immunohistochemistry.

RESULTS Median follow-up was 102.9 months. Relative to control (n = 625), for patients receiving bevacizumab-concurrent (n = 625), the hazard ratio (HR) of death was 1.06 (95% CI, 0.94 to 1.20); for bevacizumab-concurrent plus maintenance (n = 623), the HR was 0.96 (95% CI, 0.85 to 1.09). Disease-specific survival was not improved in any arm. No survival advantage was observed after censoring patients who received bevacizumab at crossover or as second line. Median OS for stage IV bevacizumab-concurrent plus maintenance was 42.8 *v* 32.6 months for stage IV control (HR, 0.75; 95% CI, 0.59 to 0.95). Relative to wild type, the HR for death for *BRCA1/2* mutated carcinomas was 0.62 (95% CI, 0.52 to 0.73), and for non-*BRCA1/2* HRR, the HR was 0.65 (95% CI, 0.51 to 0.85). *BRCA1/2*, HRR, and CD31 were not predictive of bevacizumab activity.

CONCLUSION No survival differences were observed for patients who received bevacizumab compared with chemotherapy alone. Testing for *BRCA1/2* mutations and homologous recombination deficiency is essential.

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ASSOCIATED CONTENT

Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

During 2019, the American Cancer Society estimates that approximately 22,530 women will be diagnosed with ovarian carcinoma, and approximately 13,980 patients will die as a result of the disease.[1] The prevalence is approximately 10 times its incidence, with nearly 200,000 women in the United States living with the disease at any given time. A paucity of symptoms indicative of early disease, coupled with the absence of validated screening tools, makes ovarian carcinoma the deadliest of the gynecologic malignancies, with 10-year disease-free survival rates less than 10%.[2]

Important clinical research questions include the interval from cytoreductive surgery to initiation of chemotherapy, neoadjuvant chemotherapy and timing of cytoreductive surgery, dose-dense therapy, intraperitoneal chemotherapy, heated intraoperative chemotherapy, and incorporation of targeted agents.[3-8] Although approximately 80% of patients achieve complete clinical remission through extensive cytoreductive surgery and platinum- and taxane-based antineoplastic therapy, most will experience a relapse.[2] The availability of effective and tolerable maintenance therapy that signicantly improves survival represents a high unmet clinical need.

The biology of high-grade serous carcinoma encourages early dissemination through activation of pro-angiogenic pathways.[5] A key promoter of tumor angiogenesis, vascular endothelial growth factor (VEGF), has emerged

as a validated target, with bevacizumab achieving single-agent responses of 20% in recurrent disease. Nine positive phase III randomized trials[9-17] for newly diagnosed advanced disease,[9-12] platinum-sensitive recurrence,[13-15] and platinum-resistant recurrence[16,17] have studied five different antivascular agents that target VEGF-A,[9,10,13,14,16] the VEGF receptors (VEGFR1-3),[11,12,15] or the angiopoietin/Tie2 axis[17] involved in vascular remodeling. The first trial, GOG-0218, reported a 28% reduction in the hazard of progression with integration of bevacizumab with and after chemotherapy relative to chemotherapy alone.[9] Accordingly, although it is important to optimize the role of anti-angiogenic therapy, most trials have demonstrated a more substantial improvement in progression-free survival (PFS) without significant improvement in overall survival (OS).[5] These discordant outcomes have been attributed to crossover postprogression; availability of new agents; and potential prognostic or predictive factors, including ascites formation,[18] *BRCA1/2*, and CD31 status. Here, we explore these clinical, pathologic, and molecular issues and report the final protocol-specified analysis of OS in GOG-0218.

METHODS

Patients

Women with International Federation of Gynecology and Obstetrics stage III or IV epithelial ovarian, primary peritoneal, or fallopian tube carcinoma were enrolled within 12 weeks after maximal cytoreductive surgery. Participants with stage III carcinomas were required to have gross residual disease after surgery (ie, optimal 1-cm residual or less, suboptimal more than 1 cm), and a Gynecologic Oncology Group (GOG) performance status of 0 to 2. Patients with stage III disease who had undergone complete resection were excluded, as were those with a history of vascular events or signs and symptoms of small bowel obstruction. All patients provided written informed consent. Eligibility and exclusion criteria are provided in the Data Supplement.

The master protocol is available in the Data Supplement; is registered with ClinicalTrials.gov; and was approved by the National Cancer Institute Cancer Therapy and Evaluation Program, the Central Institutional Review Board Initiative, and local institutional review boards. All carcinomas were histologically confirmed by the GOG pathology committee. The authors wrote the manuscript and are responsible for the accuracy and quality of the reported data and for the integrity of the protocol.

Study Design

GOG-0218 is an international, multicenter, double-blind, placebo-controlled, phase III trial in which two experimental arms were compared with a control arm that consisted of six 21-day cycles of intravenous carboplatin (area under the concentration *v* time curve 6) plus paclitaxel (175 mg/m^2 body surface area) followed by 16 21-day cycles of placebo. To limit wound healing complications, bevacizumab or placebo was initiated with cycle 2. The bevacizumab-concurrent arm consisted of intravenous chemotherapy as per the control arm with bevacizumab (15 mg/kg body weight) added to cycles 2 through 6. The bevacizumab-concurrent plus maintenance arm substituted bevacizumab (15 mg/kg) for placebo in cycles 7 to 22. Treatment was discontinued upon completion of all 22 cycles or with documented progression, unacceptable toxicity, or voluntary patient withdrawal.

Disease was assessed using Response Evaluation Criteria in Solid Tumors (RECIST).[19] Patients underwent computed tomography or magnetic resonance imaging of the abdomen and pelvis before cycle 1, and for those without evidence of progression, imaging was repeated after cycles 3, 6, 10, 14, 18, and 22. Serum cancer antigen 125 was obtained before each cycle for cycles 1 through 6 and at the beginning of alternate cycles for cycles 7 to 22. Radiologic evaluation was repeated every 3 months for 2 years, then every 6 months for 3 years, and then annually. The quality-of-life instruments and analysis of patient-reported outcomes are provided in the Data Supplement.

No dose reductions of bevacizumab or placebo occurred. Dose was modified only when weight changed by more than 10%. Delay and/or discontinuation of bevacizumab was predicated on the occurrence, duration, and severity of uncontrolled hypertension (defined as systolic blood pressure greater than 150 mm Hg or diastolic blood pressure greater than 90 mm Hg) and/or proteinuria (urine protein-creatinine ratio greater than 3.5). Intestinal wall disruption during cycle 2 or later, arterial thrombosis, venous thrombosis, and/or the development of reversible posterior leukoencephalopathy syndrome also led to bevacizumab discontinuation. Criteria for chemotherapy dose modifications and administration of myeloid growth factor are provided in the Data Supplement.

Statistical Analysis

The statistical analysis plan from the master protocol is available in the Data Supplement. Before random assignment, according to a 1:1:1 dynamic allocation procedure, patients were stratified by surgical debulking outcome and stage and by initial GOG performance status score (0 *v* 1 or 2).[20] Early adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) and reported until 30 days after administration of the last study treatment. Long-term adverse events of interest were submitted for up to 5 years after treatment allocation discovery.

OS was initially specified as the primary end point and defined as the observed length of life from study entry to death, regardless of cause. The study sought to determine whether the addition of five concurrent cycles of bevacizumab with or without maintenance bevacizumab increases the duration of OS compared with chemotherapy alone. To allow unblinding at progression, the primary end point was changed to PFS and reported in 2010.

The targeted accrual was 1,800 patients, with approximately 600 per arm. This would provide 90% power to detect a 23% reduction in the hazard for progression or death with either bevacizumab-containing regimen or control while limiting the overall one-sided type I error rate to 2.5%. If both experimental regimens were found to significantly increase OS relative to the control regimen, then the two investigational arms would be compared. Median survival for stage III with residual disease greater than 1 cm or stage IV was estimated to be 31 months, whereas that of stage III with macroscopic residual disease of 1 cm or less was 42 months. The final analysis of OS required at least 375 deaths in the control arm. Differences in OS among the treatment arms were assessed by a log-rank test.[21] Cox proportional hazards regression models adjusted for GOG performance status and stage were used to estimate relative hazards and provided two-sided *P* values.[22]

Molecular Biomarker Analyses

DNA was sequenced from blood and/or tumor samples for 1,195 patients and categorized as *BRCA1/2* mutated, non-*BRCA* homologous recombination repair (HRR) mutations, or wild type. Germline and somatic mutations were combined. Tumor microvessel density was measured by CD31 immunohistochemistry, and survival analyses were performed by dichotomizing the biomarker-evaluable population using median and quartile cutoffs.

RESULTS

Patients

From October 2005 to June 2009, 1,873 women were enrolled from 336 institutions in the United States, Canada, South Korea, and Japan (Fig 1). Patients were well-balanced for clinical and pathologic characteristics (Table 1). The median age was 60 years, and stage IV disease comprised approximately 25% of the patient cohort in each arm. Central pathology review confirmed high-grade serous histology in more than 80% of patients and poorly differentiated tumors in more than 70%. At a median follow-up of 17.4 months, the database was locked on February 5, 2010. We reported that the hazard of progression was reduced by approximately 28% among patients randomly assigned to the bevacizumab-concurrent plus maintenance arm relative to the control arm (median PFS, 14.1 *v* 10.3 months; hazard ratio [HR], 0.717; 95% CI, 0.625 to 0.824; $P < .001$).[9] At that time, there had been 156 deaths in the control arm (Data Supplement).

Efficacy

For the protocol-specified intention-to-treat analysis of OS, the database was locked on January 17, 2018, at a median follow-up of 102.9 months and 493 deaths in the control arm. Relative to control treatment (median OS, 41.1 months), there were no significant differences in OS among patients treated in the bevacizumab-concurrent plus maintenance arm (median OS, 43.4 months; HR, 0.96; 95% CI, 0.85 to 1.09; $P = .53$) or in the bevacizumab-concurrent arm (median OS, 40.8 months; HR 1.06; 95% CI, 0.94 to 1.20; $P = .34$; Fig 2A).

In an exploratory analysis that censored patients who died as a result of causes other than ovarian cancer or ovarian cancer treatment (n = 104), there was no survival advantage relative to the control treatment (median OS, 42.8 months) among patients randomly assigned to bevacizumab-concurrent plus maintenance (median OS, 45.6 months; HR, 0.94; 95% CI, 0.82 to 1.07; $P = .33$) or bevacizumab-concurrent (median OS, 42.3 months; HR, 1.06; 95% CI, 0.93 to 1.20; $P = .39$; Fig 2B). When censoring patients who had received bevacizumab at crossover before progression (Data Supplement) or as a second-line therapy postprogression (as a single agent or in combination with chemotherapy; Fig 2C), no significant survival differences relative to control were observed with either experimental arm.

In an exploratory subset analysis in which treatment was stratified by stage, median OS among patients with stage III disease was relatively similar at approximately 44.2 months (control), 42.9 months (bevacizumab-concurrent; HR, 1.08); and 44.3 months (bevacizumab-concurrent plus maintenance; HR, 1.05; Fig 2D). For those with stage IV disease, the control and bevacizumab-concurrent arms were associated with a median OS of 32.6 and 34.5 months, respectively (HR, 0.99). For patients with stage IV disease who received bevacizumab-concurrent plus maintenance, the median OS was 42.8 months (HR, 0.75; 95% CI, 0.59 to 0.95; Fig 2E).

Safety

Adverse events of interest were updated with long-term toxicity data (Table 2). During extended follow-up, five additional hypertensive events occurred, four of which in the bevacizumab-concurrent plus maintenance cohort. Two additional cases of proteinuria that involved two different patients treated in the bevacizumab-concurrent plus maintenance arm were also identified. Five venous thromboembolic events were reported, including one stroke in a patient treated with bevacizumab-concurrent plus maintenance, and three deep venous thromboses and one pulmonary embolism in three patients in the bevacizumab-concurrent arm. Eleven additional GI events were identified, six of which occurred in four patients treated with bevacizumab-concurrent plus maintenance, and included diarrhea, diverticulitis, enterocutaneous fistula, intestinal wall disruption, and two small bowel obstructions. There was one patient with myelodysplasia in the bevacizumab-concurrent arm and one with acute myeloid leukemia in the control arm.

Potential Prognostic and Predictive Factors

In an analysis of known clinical and pathologic prognostic markers, including age, GOG performance status, stage III, suboptimal stage III plus stage IV, presence or absence of ascites, histology, and grade, treatment with either of the bevacizumab-containing arms did not correlate with OS

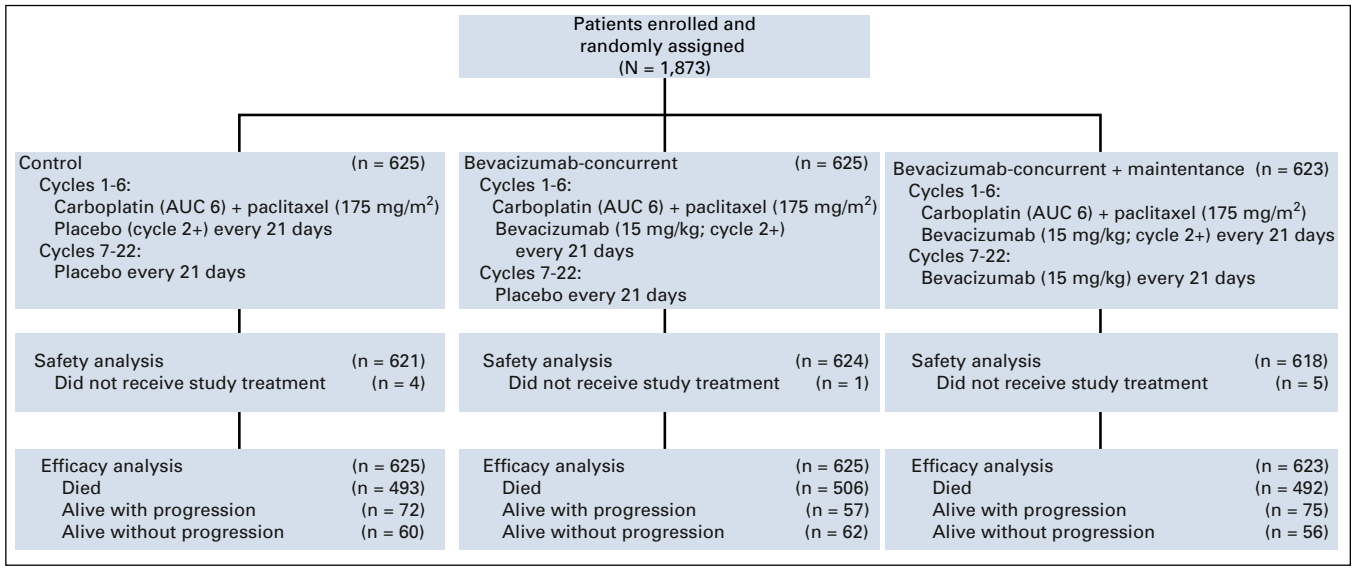


FIG 1. CONSORT diagram of the enrollment, randomization, and intention-to-treat analysis. The overall survival median follow-up for the entire study population was 102.9 months (95% CI, 100.7 to 105.9 months). As of January 17, 2018, 204 patients were alive with a progression event, and 178 patients were alive without progression; 1,491 patients died. AUC, area under the concentration *v* time curve.

(Fig 3A). No prognostic or predictive signals were observed among the 1,438 patients included in the CD31 analyses (Fig 3B; Data Supplement). Analyses of genetic categories among 1,195 blood and/or tumor samples demonstrated that relative to wild type, the HR for death as a result of *BRCA1/2* mutated carcinomas was 0.62 (95% CI, 0.52 to 0.73), and that for non-*BRCA1/2* HRR mutated carcinomas was 0.65 (95% CI, 0.51 to 0.85; Fig 4A). Although clearly prognostic, these mutations were not predictive of bevacizumab activity (Fig 4B).

Additional Exploratory Analyses

No OS benefit was observed when patients were classified according to ICON7 high-risk subgroup (suboptimally debulked stage III plus stage IV; Data Supplement). Relative to control, postprogression survival was not significantly different in either bevacizumab-containing arm (Data Supplement). The median postprogression survival for patients with stage IV disease treated in the bevacizumab-concurrent arm was 22.3 months, and for those with stage IV disease in the control arm, the median postprogression survival was 20.1 months (adjusted HR, 1.03; 95% CI, 0.81-1.30; P = 0.83). The median postprogression survival for patients with stage IV disease treated in the bevacizumab-concurrent plus maintenance arm was 23.7 months, and when compared with control treatment the adjusted HR was 0.88 (95% CI, 0.69 to 1.12; P = .28). Although not significant, the HR that compared bevacizimab-concurrent plus maintenance with control treatment flipped in the direction predicted (ie, HR < 1.00; Data Supplement).

DISCUSSION

With long-term follow-up, the protocol-specified stipulations for maturation of the OS end point demonstrate no evidence of a survival benefit with bevacizumab. Although the PFS end point led to European Medicines Agency approval of frontline bevacizumab in the European Union in 2011, the US Food and Drug Administration's (FDA's) November 18, 2011 decision to revoke accelerated approval of bevacizumab for metastatic breast cancer (partly because of a lack of OS benefit) had a negative impact on registration trials in ovarian cancer.

The clinical relevance of PFS continues to be debated, with many investigators recognizing that PFS is sensitive to cytostatic agents designed to stabilize tumors through inhibition of cell division and growth. Therefore, PFS only reflects the clinical impact of an investigational agent during its administration. Although OS benefit has been reported with incorporation of paclitaxel, intraperitoneal chemotherapy, dose-dense paclitaxel, and heated intraoperative chemotherapy, most trials, including follow-up studies of intraperitoneal and dose-dense therapy, have not reported improved OS.[2] In the recurrent setting, OS has been elusive, even in studies with initial signals that suggest benefit. Because ovarian cancer may retain chemosensitivity for a period of time, most patients receive multiple lines of treatment for recurrent disease where platinum sensitivity, the treatment-free interval, number of lines of prior therapy, tumor histology, and molecular signature are important considerations.[23] Unanticipated crossover, nonuniformity of postprogression therapy, and duration of postprogression survivorship may obscure the OS impact of novel agents. In recent years, the FDA has acknowledged that PFS, when accompanied by other measures of clinical value (eg, quality of life), can be persuasive.[24] Still, the lack of survival benefit (even when adjusting for disease-specific mortality or second-line bevacizumab) is problematic, particularly in the absence of validated predictive biomarkers.

TABLE 1. Clinical, Pathologic, and Molecular Characteristics of the Study Population According to Treatment Group

	Treatment Group, No. (%)		
Characteristic	**Bevacizumab-Concurrent Plus Maintenance**	**Control**	**Bevacizumab-Concurrent**
No. of patients	623	625	625
Age, years			
Median	60	60	60
Range	22-89	25-86	24-88
Race			
Non-Hispanic white	521 (83.6)	526 (84.2)	519 (83.0)
Asian	39 (6.3)	41 (6.6)	37 (5.9)
Non-Hispanic black	27 (4.3)	25 (4.0)	28 (4.5)
Hispanic	25 (4.0)	21 (3.4)	28 (4.5)
Other or unspecified	11 (1.8)	12 (1.9)	13 (2.1)
GOG performance status			
0	305 (49.0)	311 (49.8)	315 (50.4)
1	267 (42.9)	272 (43.5)	270 (43.2)
2	51 (8.2)	42 (6.7)	40 (6.4)
FIGO stage/debulking status			
III (optimal; ≤ 1 cm)	216 (34.7)	218 (34.9)	205 (32.8)
III (suboptimal; > 1 cm)	242 (38.8)	254 (40.6)	256 (41.0)
IV	165 (26.5)	153 (24.5)	164 (26.2)
Ascites			
Yes	445 (71.4)	454 (72.6)	460 (73.6)
No	165 (26.5)	154 (24.6)	141 (22.6)
Unknown	13 (2.1)	17 (2.7)	24 (3.8)
Tumor histology			
Serous adenocarcinoma	524 (84.1)	541 (86.6)	519 (83.0)
Endometrioid adenocarcinoma	24 (3.9)	21 (3.4)	14 (2.2)
Clear cell adenocarcinoma	20 (3.2)	12 (1.9)	23 (3.7)
Mucinous adenocarcinoma	8 (1.3)	6 (1.0)	5 (0.8)
Other or unspecified	47 (7.5)	45 (7.2)	64 (10.2)
Tumor grade			
Poorly differentiated	460 (73.8)	445 (71.2)	465 (74.4)
Moderately differentiated	97 (15.6)	102 (16.3)	86 (13.8)
Well differentiated	18 (2.9)	36 (5.8)	28 (4.5)
Not graded	48 (7.7)	42 (6.7)	46 (7.4)
Mutations*			
BRCA1	61 (15.2)	53 (13.0)	34 (8.8)
BRCA2	31 (7.7)	28 (6.9)	19 (4.9)
HRR	28 (7.0)	27 (6.6)	26 (6.7)
Wild type/no mutation	281 (70.1)	300 (73.5)	307 (79.5)
CD31†			
≤ Median	239 (48.6)	247 (51.1)	237 (51.2)
> Median	253 (51.4)	236 (48.9)	226 (48.8)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; GOG, Gynecologic Oncology Group; HRR, homologous recombination repair.

*Includes germline and somatic. Sample size includes 1,195 patients.

†Dichotomized by the median. Sample size includes 1,438 patients.

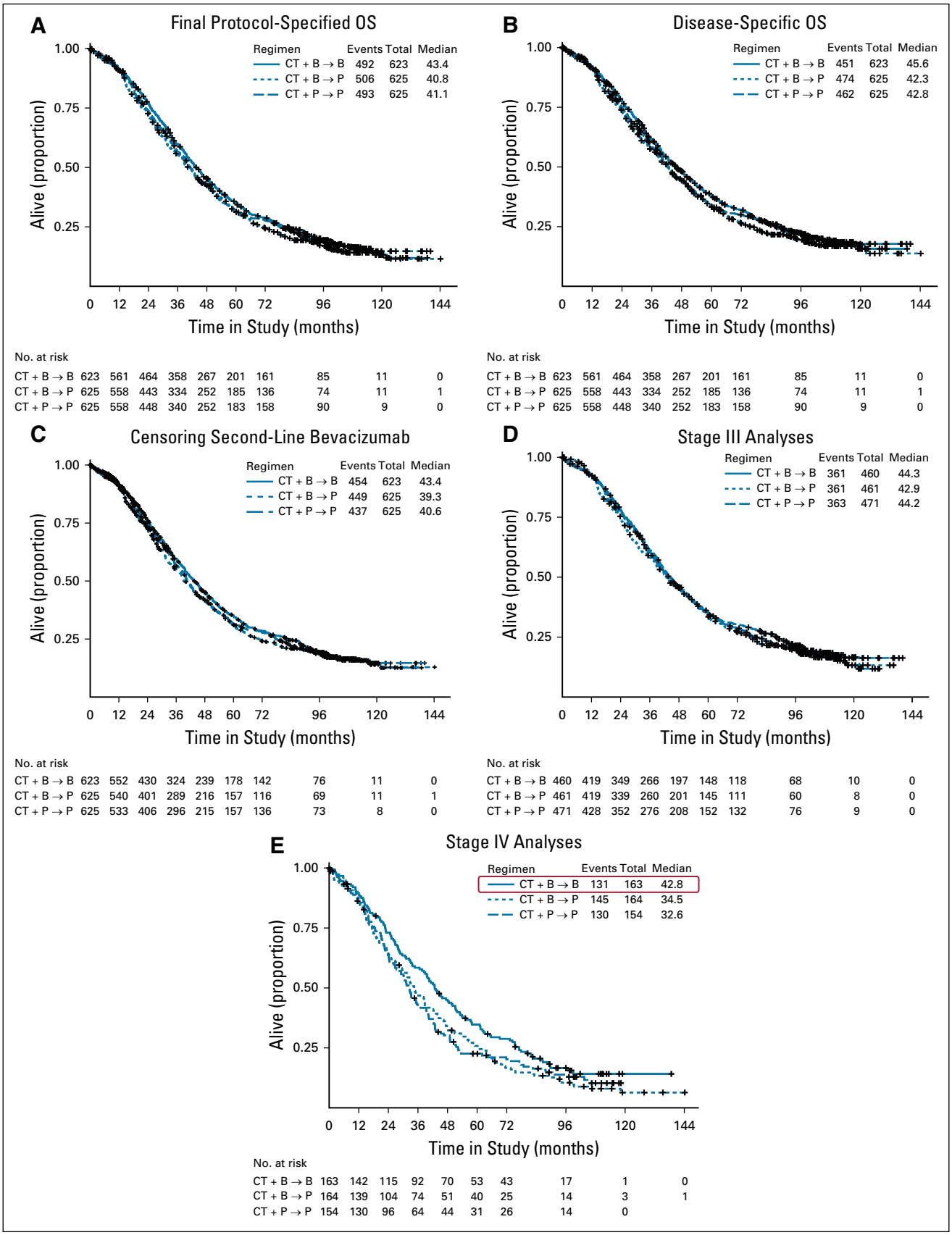


FIG 2. Kaplan-Meier curves that compare overall survival (OS) of the various treatment arms studied in GOG-0218. Database lock was January 17, 2018. (A) Final protocol-specified OS according to treatment arm. Overall median follow-up was 102.9 months (continued on following page)

TABLE 2. Long-Term Toxicology Involving Adverse Events of Interest According to Treatment Group

	Treatment Group, No. (%)		
Adverse Event	**Bevacizumab Concurrent Plus Maintenance**	**Control**	**Bevacizumab-Concurrent**
No. of patients	608	601	607
GI events (grade ≥ 2)	22 (3.6)	10 (1.7)	19 (3.1)
Hypertension (grade ≥ 2)	140 (23.0)	43 (7.2)	101 (16.6)
Proteinuria (grade ≥ 3)	12 (2.0)	4 (0.7)	4 (0.7)
Pain (grade ≥ 2)	286 (47.0)	251 (41.8)	254 (41.8)
Neutropenia (grade ≥ 4)	386 (63.5)	347 (57.7)	384 (63.3)
Febrile neutropenia	27 (4.4)	21 (3.5)	30 (4.9)
Venous thromboembolism	42 (6.9)	35 (5.8)	36 (5.9)
Arterial thromboembolism	4 (0.7)	5 (0.8)	4 (0.7)
Wound disruption	18 (3.0)	17 (2.8)	22 (3.6)
CNS bleeding	2 (0.3)	0	0
Non-CNS bleeding (grade ≥ 3)	13 (2.1)	5 (0.8)	8 (1.3)
RPLS	1 (0.2)	0	2 (0.3)
Acute myeloid leukemia/MDS	0	1 (0.2)	1 (0.2)

Abbreviations: MDS, myelodysplastic syndrome; RPLS, reversible posterior leukoencephalopathy syndrome.

Although the prognostic impact of *BRCA1/2* mutations generally has been accepted, this randomized trial is the first in our knowledge to demonstrate the effect so clearly. However, molecular biomarkers, including *BRCA1/2*, non-*BRCA1/2* HRR mutations, and CD31, previously reported to have prognostic significance for both PFS and OS[25,26] did not predict bevacizumab activity. An earlier report suggested overexpression of endothelial cell protein CD31 (which lines newly formed blood vessels) to be prognostic, but that analysis had been derived from earlier database locks when survival data were not mature.[26]

(Continued). (95% CI, 100.7 to 105.9 months). In the 1,873 patients who comprised the entire study population, 1,491 died, 204 were alive with a progression event, and 178 were alive without progression. Median follow-up for the control cohort (carboplatin and paclitaxel plus placebo followed by placebo [CT + P → P]) was 103.4 months (95% CI, 100.4 to 107.9 months). In 625 patients, 565 experienced a progression event, and 493 died; 72 were alive with a progression event, and 60 were alive without progression. Median follow-up for the bevacizumab-concurrent cohort (carboplatin and paclitaxel plus bevacizumab followed by placebo [CT + B → P]) was 102.3 months (95% CI, 98.8 to 106.5 months). In 625 patients, 563 experienced a progression event, and 506 died; 57 were alive with a progression event, and 62 were alive without progression. The hazard ratio (HR) for bevacizumab-concurrent *v* control stratified by stage and Gynecologic Oncology Group (GOG) performance status was 1.06 (95% CI, 0.94 to 1.20; $P = .34$). Median follow-up for the bevacizumab-concurrent plus maintenance cohort (carboplatin and paclitaxel plus bevacizumab followed by bevacizumab [CT + B → B]) was 101.9 months (95% CI, 98.7 to 107.4 months). In 623 patients, 567 experienced a progression event, and 492 died; 75 were alive with a progression event, and 56 were alive without progression. The HR for death for bevacizumab-concurrent plus maintenance *v* control stratified by stage and GOG performance status was 0.96 (95% CI, 0.85 to 1.09; $P = .53$). (B) Disease-specific OS according to treatment arm. Patients who died as a result of causes other than disease or treatment-related causes were censored. Overall, the number of deaths reduced from 1,491 to 1,387 (change of 104; 7.0%). In the control arm, the number of deaths reduced from 493 to 462 (change of 31; 6.3%). In the bevacizumab-concurrent arm, the number of deaths reduced from 506 to 474 (change of 32; 6.3%). In the bevacizumab-concurrent plus maintenance arm, the number of deaths reduced from 492 to 451 (change of 41; 8.3%). The HR for bevacizumab-concurrent *v* control stratified by stage and GOG performance status was 1.06 (95% CI, 0.93 to 1.20; $P = .39$). The HR for death for bevacizumab-concurrent plus maintenance *v* control stratified by stage and GOG performance status was 0.94 (95% CI, 0.82 to 1.07; $P = .33$). (C) Final OS according to treatment arm after censoring those who received bevacizumab as a second line of therapy. Overall, 184 patients received bevacizumab as a second-line therapy after progression. When measuring OS since the time patients initiated treatment (n = 205), the HR for bevacizumab-concurrent *v* control stratified by stage and GOG performance status and after censoring those who received bevacizumab postprogression was 1.05 (95% CI, 0.92 to 1.20; $P = .49$). The HR for death for bevacizumab-concurrent plus maintenance *v* control stratified by stage and GOG performance status and after censoring those who received bevacizumab postprogression was 0.96 (95% CI, 0.84 to 1.09; $P = .52$). (D) Final OS according to treatment arm and stratified by International Federation of Gynecology and Obstetrics stage III. Survival of patients with stage III disease was similar in all three treatment arms. Relative to control, the HR for death for bevacizumab-concurrent was 1.08 (95% CI, 0.93 to 1.25), and that of bevacizumab-concurrent plus maintenance was 1.05 (95% CI, 0.91 to 1.22). (E) Final OS according to treatment arm and stratified by International Federation of Gynecology and Obstetrics stage IV. Relative to control, the HR for death of bevacizumab-concurrent was 0.99 (95% CI, 0.78 to 1.26), whereas that of bevacizumab-concurrent plus maintenance was 0.75 (95% CI, 0.59 to 0.95). Note that in this exploratory analysis, the survival of patients with stage IV disease treated in the bevacizumab-concurrent plus maintenance arm (box) approximated that observed for patients with stage III disease (as in panel D).

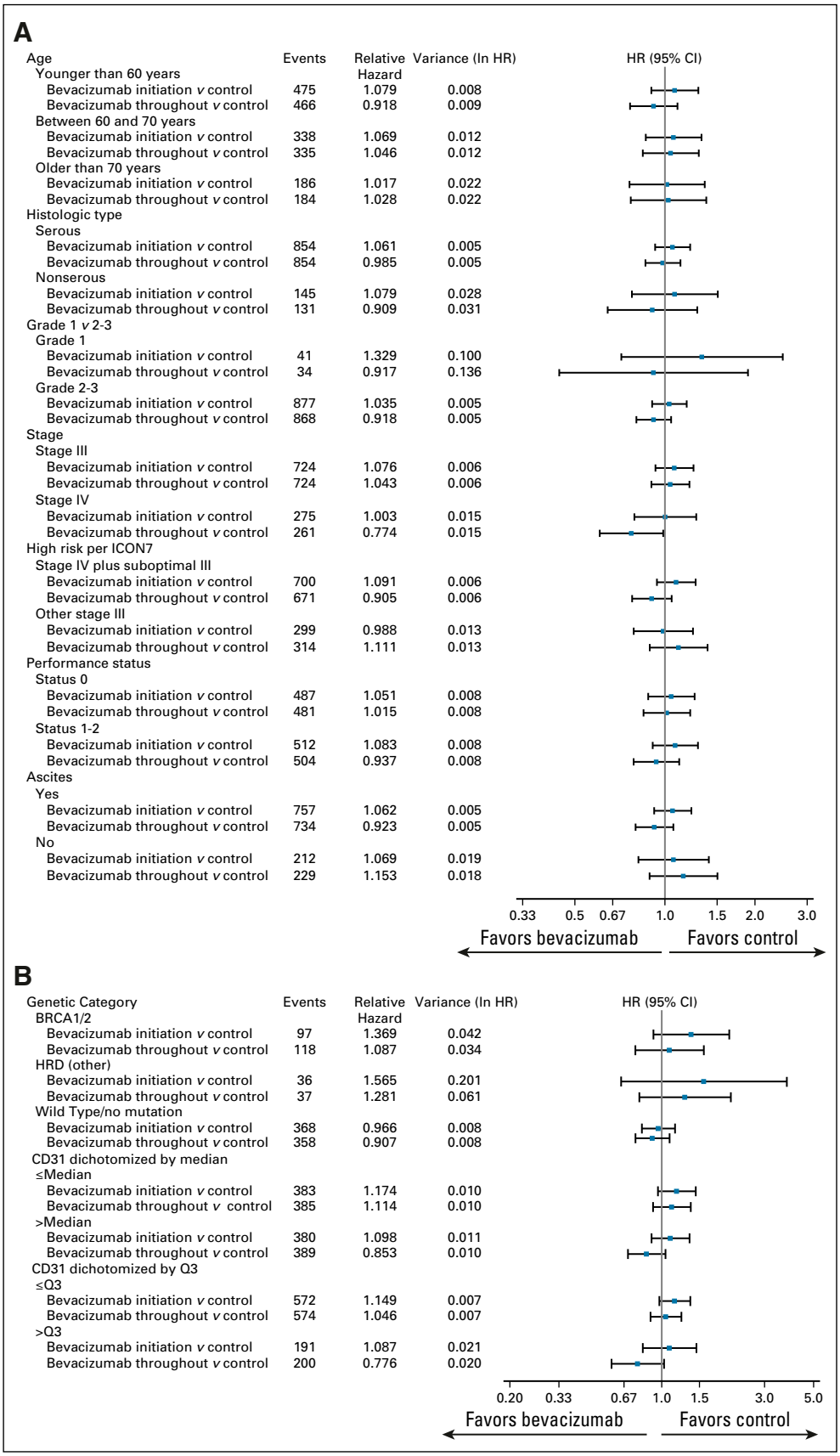
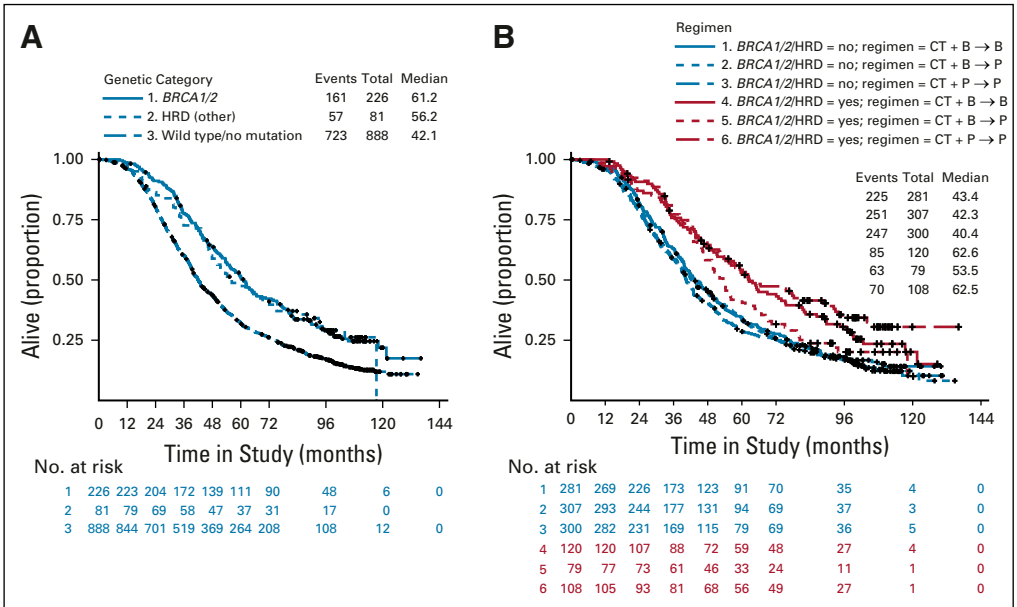


FIG 3. Analysis of prognostic factors. (A) Forest plot of clinical and pathologic prognostic factors (N = 1,873). (B) Forest plot of molecular prognostic biomarkers. The sample size for the genetic category analysis was 1,195 blood and tumor samples. Patients were categorized into three genetic categories: *BRCA1/2*, homologous recombination repair mutations, or wild type (no mutation). For the forest plots, *BRCA1/2* and homologous recombination repair mutations were depicted as separate categories. The sample size for the CD31 analysis was 1,438 blood and tumor samples. HR, hazard ratio; HRD, homologous repair deficiency; Q3, quartile 3.



	BRCA Mutations		HRR Mutations (non-BRCA1/2)													
Germline	*BRCA1*	*BRCA2*	*ATM*	*ATR*	*BARD1*	*BLM*	*BRIP1*	*CHEK2*	*MRE11A*	*NBN*	*PALB2*	*RAD51C*	*RAD51D*	*RBBP8*	*SLX4*	*XRCC2*
	148	78	12	5	3	5	19	2	2	3	6	7	7	8	2	3
Somatic*	*BRCA1*	*BRCA2*	*ATM*	*ATR*	*BARD1*	*BLM*	*BRIP1*	*CHEK2*	*MRE11A*	*NBN*	*PALB2*	*RAD51C*	*RAD51D*	*RBBP8*	*SLX4*	*XRCC2*
	17	7	—	3	—	2	—	—	—	—	—	—	—	3	—	—

FIG 4. Analyses of *BRCA1/2* and homologous recombination deficiency (HRD) according to final overall survival. (A) Kaplan-Meier survival curves demonstrate the prognostic impact of mutations in genes involved in homologous recombination. Of the 1,873 patients studied in GOG-0218, 1,195 provided blood or tumor samples to be sequenced and were able to be categorized into three genetic categories: breast cancer susceptibility gene 1/2 (*BRCA1/2*), homologous recombination repair (HRR) mutations, or wild type (no mutation). Using wild type as the reference, the hazard ratio (HR) for death for *BRCA1/2* was 0.62 (95% CI, 0.52 to 0.73) and for death for HRR mutations, 0.65 (95% CI, 0.51 to 0.85). (B) Kaplan-Meier survival curves that demonstrate the effect of treatment allocation on overall survival stratified by genetic category. Although *BRCA1/2* and HRR mutations were associated with improved prognosis, their occurrence did not predict bevacizumab activity. For graphic purposes, *BRCA1/2* and HRR were combined into one category. For the patients who were *BRCA*/HRR negative (ie, wild type), the HR for death in those treated with bevacizumab-concurrent plus maintenance (carboplatin and paclitaxel plus bevacizumab followed by bevacizumab [CT + B → B]) relative to control (carboplatin and paclitaxel plus placebo followed by placebo [CT + P → P]) and stratified by stage and Gynecologic Oncology Group (GOG) performance status was 0.89 (95% CI, 0.74 to 1.07); the HR for death in those treated with bevacizumab-concurrent (carboplatin and paclitaxel plus bevacizumab followed by placebo [CT + B → P]) relative to control and stratified by stage and GOG performance status was 0.96 (95% CI, 0.80 to 1.15). For the patients who had *BRCA*/HRR mutations, the HR for death in those treated with bevacizumab-concurrent plus maintenance relative to control and stratified by stage and GOG performance status was 1.18 (95% CI, 0.86 to 1.63); the HR for death in those treated with bevacizumab-concurrent relative to control and stratified by stage and GOG performance status was 1.44 (95% CI, 1.02 to 2.02). (*) Germline wild type: *BRCA1/2*; ataxia-telangiectasia mutated (*ATM*); ataxia telangiectasia and Rad3 related (*ATR*); BRCA1-associated RING domain 1 (*BARD1*); Bloom DNA helicase (*BLM*); BRCA1 interacting protein C-terminal helicase 1 (*BRIP1*); checkpoint kinase 2 (*CHEK2*); MRE11 meiotic recombination 11 homolog A (*MRE11A*; *Saccharomyces cerevisiae*); nibrin (*NBN*); partner and localizer of BRCA2 (*PALB2*); RAD51 homolog C (*RAD51C*; *S cerevisiae*); RAD51 homolog D (*RAD51D*); RB binding protein 8, endonuclease (*RBBP8*); structure-specific endonuclease subunit homolog (*SLX4*; *S cerevisiae*); and x-ray repair cross complementing 2 (*XRCC2*).

The FDA ultimately approved frontline and maintenance bevacizumab for advanced ovarian cancer on June 13, 2018. Because the December 19, 2018, approval of olaparib in patients with newly diagnosed germline or somatic *BRCA1/2* mutations on the basis of SOLO-1 (ClinicalTrials.gov identifier: NCT01844986)[27] is for maintenance alone, the approval for bevacizumab represents the first new primary treatment indication for ovarian cancer in the United States in more than two decades.

In the ICON7 randomized trial of frontline bevacizumab, a survival benefit was observed in an exploratory analysis of a high-risk subgroup (suboptimal stage III and stage IV).[28]

Although we were unable to validate the European trial's findings in our placebo-controlled trial, our exploratory analysis suggests that bevacizumab, when administered with and after chemotherapy, may be beneficial for patients with stage IV disease by producing median survival rates that approximate those observed with more-favorable stage III tumors (Figs 2D and 2E). Although not preplanned, the observed 10-month relative survival benefit mirrors that reported for the ICON7 high-risk subgroup.[28]

Bevacizumab with chemotherapy also has been approved for platinum-resistant and platinum-sensitive recurrent disease. Although a significant negative rebound effect on postprogression survival has not been observed, the sequencing of drug can be explored. Because novel combinations (including combined anti-angiogenesis and vascular disrupting agents)[29] are being studied in the recurrent setting, it becomes paramount to identify a molecular signature that drives anti-angiogenesis therapy and to clarify the role of bevacizumab in this disease.

Several phase III randomized trials that may influence frontline maintnance therapy are ongoing, including PRIMA (study of niraparib maintenance treatment in the homologous recombination deficiency population; ClinicalTrials.gov Identifier: NCT02655016), VELIA (study of veliparib combined with and following chemotherapy; ClinicalTrials.gov Identifier 02470585), and PAOLA-1 (bevacizumab with and without olaparib; ClincialTrials.gov identifier: NCT02477644; Data Supplement). The drive to study novel combinations and their potential commercial availability heralds significant financial toxicity.[30] Whether bevacizumab biosimilars (eg, bevacizumab-awwb) can curtail costs to the degree required by society is not certain. The regulatory approval of bevacizumab for newly diagnosed ovarian cancer needs to be framed against a backdrop devoid of predictive biomarkers for anti-VEGF therapy.

The absence of a survival advantage associated with bevacizumab therapy and the new exploratory analyses provide valuable concluding information on a pivotal trial of anti-angiogenesis therapy in patients with newly diagnosed ovarian cancer. We also have confirmed within a randomized trial the importance of genetic testing. This has major implications for the design of future trials, which (on the basis of recent data) should include a provision to track *BRCA1/2* reversions.[31] Unfortunately, many patients with ovarian cancer are not being tested for *BRCA1/2*.[32] Strategies to optimize *BRCA* testing in affected populations[33] and the development of a clinical platform for homologous recombination deficiency testing are implicit.

Because a potential survival advantage may have been obscured by crossover and/or receipt of varied postprogression therapy, OS is less relevant in GOG-0218, and PFS has clinically meaningful value. For patients with stage III disease, GOG-0218 informs clinical practice. For stage IV disease, our exploratory analysis suggests a survival benefit that also may be supported by the high-risk subgroup analysis from ICON7. Because recent trials have failed to confirm a survival benefit with dose-dense paclitaxel, patients previously considered to be suitable candidates for nonstandard dosing may opt for bevacizumab, particularly in light of the GOG-0262 subset analysis that demonstrated possible antagonism when bevacizumab is used in conjunction with dose-dense therapy.[34-37] Finally, GOG-0252 was the first phase 3 randomized trial to isolate the effect of intraperitoneal chemotherapy, and having failed to meet its primary endpoint, frontline concurrent and maintenance bevacizumab may obviate the need for intraperitoneal therapy.[38] After primary resection, patients without contraindications to anti-angiogenesis therapy may consider postoperative chemotherapy with bevacizumab, during which time germline and (if necessary) somatic *BRCA1/2* testing can be performed. Patients with *BRCA1/2* mutated carcinoma can be transitioned to maintenance olaparib, whereas those without mutations may remain on maintenance bevacizumab.

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Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer

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