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ORIGINAL REPORT

OCEANS: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Chemotherapy With or Without Bevacizumab in Patients With Platinum-Sensitive Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

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ABSTRACT

Purpose
This randomized, multicenter, blinded, placebo-controlled phase III trial tested the efficacy and safety of bevacizumab (BV) with gemcitabine and carboplatin (GC) compared with GC in platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer (ROC).

Patients and Methods
Patients with platinum-sensitive ROC (recurrence ≥ 6 months after front-line platinum-based therapy) and measurable disease were randomly assigned to GC plus either BV or placebo (PL) for six to 10 cycles. BV or PL, respectively, was then continued until disease progression. The primary end point was progression-free survival (PFS) by RECIST; secondary end points were objective response rate, duration of response (DOR), overall survival, and safety.

Results
Overall, 484 patients were randomly assigned. PFS for the BV arm was superior to that for the PL arm (hazard ratio [HR], 0.484; 95% CI, 0.388 to 0.605; log-rank $P < .0001$); median PFS was 12.4 *v* 8.4 months, respectively. The objective response rate (78.5% *v* 57.4%; $P < .0001$) and DOR (10.4 *v* 7.4 months; HR, 0.534; 95% CI, 0.408 to 0.698) were significantly improved with the addition of BV. No new safety concerns were noted. Grade 3 or higher hypertension (17.4% *v* < 1%) and proteinuria (8.5% *v* < 1%) occurred more frequently in the BV arm. The rates of neutropenia and febrile neutropenia were similar in both arms. Two patients in the BV arm experienced GI perforation after study treatment discontinuation.

Conclusion
GC plus BV followed by BV until progression resulted in a statistically significant improvement in PFS compared with GC plus PL in platinum-sensitive ROC.

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INTRODUCTION

The expected incidence of epithelial ovarian cancer in women in the United States in 2012 is approximately 22,280 (15,500 deaths) and in Europe in 2008 was estimated at 69,565 patient cases (44,280 deaths). [1,2] At diagnosis, most women present with advanced disease, which accounts for the high mortality rate. Despite initial treatment with debulking surgery and taxane and platinum-based chemotherapy, the majority of patients will relapse.[3] Disease that relapses ≥ 6 months after completion of initial therapy is considered platinum sensitive, and re-treatment with platinum-based chemotherapy is an important part of managing these patients.[4-6]

The combination of gemcitabine and carboplatin (GC) for platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer (ROC) was approved by regulatory agencies in several European countries in 2004 and the US Food and Drug Administration in 2006 based on an intergroup (Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom [AGO-OVAR] –National Cancer Institute of Canada Clinical Trials Group [NCIC

CTG]–European Organisation for Research and Treatment of Cancer [EORTC]) phase III study. This study reported a statistically significant improvement in progression-free survival (PFS) for GC compared with C alone. The median PFS for the GC arm was 8.6 months versus 5.8 months for the control arm (hazard ratio [HR], 0.72; 95% CI, 0.58 to 0.90; $P = .0031$).[5]

Bevacizumab (BV), a monoclonal antibody targeting vascular endothelial growth factor (VEGF-A), has demonstrated activity in three phase II studies in ROC. The GOG (Gynecologic Oncology Group) 170D study evaluated single-agent BV at 15 mg/kg every 3 weeks in 62 patients who had received one to two prior regimens.[7] The objective response rate (ORR) was 21% (90% CI, 12.9% to 31.3%), with a median duration of response (DOR) of 10.3 months. Twenty-five patients (40.3%; 90% CI, 29.8% to 53.6%) were progression free for $\geq$ 6 months ($PF_{6\ months}$). No GI perforations (GIPs) were reported. In another single-arm study, 70 patients with one to three prior regimens received BV with metronomic cyclophosphamide and demonstrated a 24% ORR (95% CI, 15% to 36%), with a $PF_{6\ months}$ rate of 56% (95% CI, 44% to 67%).[8] GIP or fistula was reported in 5.7% of patients (four of 70). These two studies enrolled patients with platinum-sensitive and platinum-resistant disease. A third study evaluated BV alone in 44 patients with platinum-refractory or platinum-resistant disease (two to three prior regimens and progression during or within 3 months of treatment with topotecan or pegylated liposomal doxorubicin).[9] This study showed an ORR of 15.9% (95% CI, 7.2% to 29%), with 27.8% of patients achieving $PF_{6\ months}$. Although BV seemed to be active in this heavily pretreated, refractory population, a higher-than-expected incidence of GIPs (five of 44 patients; 11.4%) led to early closure of the study.

On the basis of data supporting the activity of BV in ROC, and with close attention to the GIP concerns raised by the phase II study in platinum-resistant patients, OCEANS (Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease), a randomized, double-blind, phase III trial, was initiated to compare the efficacy and safety of GC plus BV (BV arm) and GC plus placebo (PL arm) in patients with platinum-sensitive ROC.

PATIENTS AND METHODS

Eligibility Criteria

Eligible patients were $\geq$ 18 years of age with histologically confirmed ROC and disease progression $\geq$ 6 months after completion of front-line platinum-based chemotherapy. No prior chemotherapy in the recurrent setting was allowed. Patients were required to have measurable disease according to RECIST version 1.0.[10] Other key eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 or 1[11]; life expectancy of at least 12 weeks; adequate bone marrow, coagulation, renal, and hepatic function; and signed, approved informed consent in accordance with federal, state, and local requirements as well as authorization permitting the release of personal health information.

Patients were ineligible if they met any of the following criteria: prior treatment with BV or other VEGF pathway–targeted therapy; other malignancies within 5 years (unless low risk of recurrence); history of abdominal fistula, GIP, or intra-abdominal abscess; clinical signs or symptoms of GI obstruction and/or requirement for parenteral hydration or nutrition; nonhealing wound, ulcer, or bone fracture; bleeding diathesis or significant coagulopathy; known CNS disease (except for treated brain metastases); clinically significant cardiovascular disease; and a major surgical procedure within 28 days of enrollment or anticipated to occur while participating in study.

Procedures

Eligible patients were randomly assigned to the BV or PL arm using an interactive voice response system in a one-to-one ratio; randomization was stratified by time from last platinum treatment to recurrence (6 to 12 *v* > 12 months) and cytoreductive surgery for ROC (yes *v* no). The study sponsor (Genentech, South San Francisco, CA), contract research organization, investigators, and patients were blinded to treatment assignment. At the time of documented progressive disease (PD), patients could be unblinded to treatment assignment at the request of the investigator.

The trial was initiated as a phase II study, with extensive safety reviews focused on GI toxicity. The data monitoring committee conducted periodic reviews of unblinded safety summaries prepared by an external statistical data coordinating center and had planned additional extensive reviews if more GIPs were observed in the BV versus PL arm after at least 10 weeks of treatment. After approximately 20 patients were accrued to each arm, and no GIP events were reported after > 10 weeks of follow-up, the trial was converted to a phase III trial.

Treatment Plan and Dose Modification

The GC doses, schedule, and allowed number of cycles were matched to those of the AGO-OVAR–NCIC CTG–EORTC trial.[5] Patients received G 1,000 mg/m^2 on days 1 and 8 and C area under the curve 4 mg/mL/min on day 1 (based on the Calvert formula).[12,13] Cycles were repeated every 21 days. The trial was designed so that patients would receive six cycles of GC but would be allowed to receive up to 10 cycles if continued response was documented. BV or PL 15 mg/kg was administered intravenously on day 1 of each cycle, before GC. After completion of GC, either BV or PL, respectively, was continued until PD or unacceptable toxicity.

Treatment on day 1 of each cycle was held if the absolute neutrophil count was < 1,500, hemoglobin count < 8.5, or platelets < 100,000 within 24 hours of scheduled treatment. Cycles could be delayed for a maximum of 3 weeks until these values were achieved. On day 8, dose modifications and treatment with G were administered according to the G package insert[14] and protocol (Data Supplement). BV or PL could be held for toxicity for a maximum of 6 weeks to allow recovery. If BV or PL was held for longer than 6 weeks, the trial protocol required the discontinuation of BV. In the event that a component of therapy had to be discontinued because of toxicity, the patient was eligible to continue with the other components per protocol (Data Supplement).

Patient Assessment

The assessment of progression was based on radiologic evaluation according to RECIST version 1.0. Progression could be determined clinically by symptomatic progression but not by cancer antigen 125 (CA-125) elevation alone. All patients were required to undergo computed tomography scans every 9 weeks from day 1 of cycle 1, regardless of whether treatment was delayed or discontinued or whether a scan was performed off schedule. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 3.0. Patients were observed for adverse events for 30 days after treatment discontinuation and for survival every 3 months until death.

Statistical Analyses

The primary outcome measure was PFS, as determined by investigators. Secondary outcome measures were ORR, overall survival (OS), and DOR. A sensitivity analysis was performed for PFS determined by an independent review committee (IRC).

PFS was defined as the time from random assignment to PD or death as a result of any cause. For patients alive without documented PD at the time of the analysis, PFS was censored at the time of the last tumor assessment. If no postbaseline assessment was performed, the date of random assignment plus 1 day was used as the censor date. OS was defined as the time from random assignment until death as a result of any cause, and patients alive at the time of the analysis were censored at the date of last contact. In the ORR analysis, patients without a postbaseline assessment were considered to be nonresponders. In the IRC-determined analysis, PFS was defined as the time from random assignment until PD (IRC determined) or on-study death (ie, death within 9 weeks of the last dose of protocol treatment).

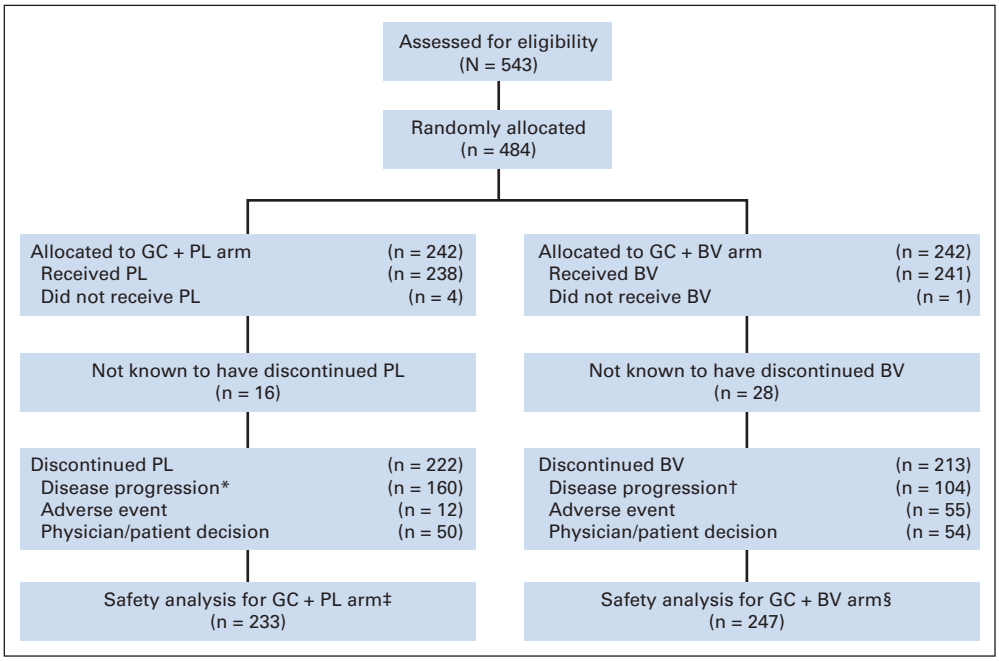

Fig 1. CONSORT diagram of all randomly assigned patients (represents intent-to-treat population). BV, bevacizumab; GC, gemcitabine plus carboplatin; PL, placebo. (*) Includes 158 patients with disease progression per RECIST and two patients with clinical disease progression. (†) Includes 100 patients with disease progression per RECIST and four patients with clinical disease progression. (‡) Five patients who were randomly assigned to the GC plus PL arm received one or two doses of BV in error and were assigned to the GC plus BV arm for all safety analyses. Four patients who were randomly assigned to the GC plus PL arm did not receive any protocol treatment and thus were not included in the safety analyses. (§) Five patients who were randomly assigned to the GC plus PL arm received one or two doses of BV in error and were assigned to the GC plus BV arm for all safety analyses.

To detect an HR of 0.73 for PFS in the BV arm relative to the PL arm, approximately 317 events were required. A two-sided log-rank test at the .05 level of significance with 80% power was assumed in the calculation. Per agreement with regulatory authorities, two interim OS analyses were planned: one at the time of final PFS analysis and the other at approximately 214 deaths. The final OS analysis will be conducted at 353 deaths.

Kaplan-Meier methodology[15] was applied to estimate the median PFS and DOR for each treatment group. Brookmeyer-Crowley methodology[16] was used to construct 95% CIs for median values. The stratified HR was estimated using a Cox regression model. Stratification factors were time to recurrence since the last platinum therapy (6 to 12 *v* > 12 months) and cytoreductive surgery for recurrent disease (yes *v* no). A two-sided stratified log-rank test was used to compare the two groups. ORRs were compared by the Cochran-Mantel-Haenszel test. Efficacy analyses were performed on the intent-to-treat population, and the safety population consisted of all randomly assigned patients who received at least one partial dose of any component of protocol treatment.

RESULTS

Patient Characteristics

From April 2007 through January 2010, 484 patients were randomly assigned. Patient disposition is shown in Figure 1. The treatment arms were well balanced for baseline patient and disease characteristics (Table 1).

Treatment Administration

The median number of cycles of GC in both arms was six (range, one to 10). The median numbers of cycles of PL and BV were 10 (range, one to 36) and 12 (range, one to 43), respectively.

Efficacy

At the time of the final PFS analysis (338 events), the median follow-up was 24 months. The addition of BV to GC led to a statistically significant increase in PFS compared with PL, with an HR of 0.484 (95% CI, 0.388 to 0.605; log-rank $P < .0001$; Fig 2). The median PFS was 8.4 and 12.4 months for the PL and BV arms, respectively. Subgroup analyses examining age, baseline Eastern Cooperative Oncology Group performance status, platinum-free interval (6 to 12, 12 to 24, and > 24 months), and cytoreductive surgery for recurrent disease all supported the primary analysis, demonstrating significantly improved PFS in the BV arm (Fig 3). Improvements in PFS were confirmed by the IRC analysis, which showed an HR of 0.451 (95% CI, 0.351 to 0.580; $P < .0001$) and an increase in median PFS from 8.6 to 12.3 months (Fig 4).

There was also a statistically significant improvement in ORR of 21.1% in the BV arm (ORR, 78.5% [190 of 242] *v* 57.4% [139 of 242]; $P < .0001$). The majority of responses in both the PL (48.3% [117 of 242]) and BV (61.2% [148 of 242]) arms were partial responses. The DOR for responders in the PL arm was 7.4 months compared with 10.4 months in the BV arm (HR, 0.534; 95% CI, 0.408 to 0.698).

In both arms, the most common reason for treatment discontinuation was PD: 66.1% and 43.0% in the PL and BV arms, respectively (Fig 1). In the PL arm, 158 (65.3%) had RECIST-defined PD, and two (0.8%) had clinical PD; in the BV arm, 100 patients (41.3%) had RECIST-defined PD, and four (1.7%) had clinical PD.

With regard to OS, at the time of the final PFS analysis, the data were immature, with 141 deaths (29% of patients), and an additional analysis was conducted with a data cutoff date of August 29, 2011. These results, based on 235 deaths (48.6% of patients), are shown in Table 2; the majority of deaths resulted from disease progression. The median OS for the PL arm was 35.2 months, and the median OS for the BV arm was 33.3 months. These data remain immature, with a high degree of censoring beyond 18 months and a longer-than-expected median OS in both arms. The updated analysis also evaluated the use of subsequent treatment; with data available to date, 88% (PL arm) and 84% (BV arm) of patients received subsequent anticancer therapy, including bevacizumab in 31% (PL arm) and 15% (BV arm) of patients.

Table 1. Baseline Patient Demographics and Disease Characteristics*

Characteristic	GC + PL (n = 242) No.	%	GC + BV (n = 242) No.	%
Age, years				
Mean	61.6		60.5	
SD	10.2		9.8	
Median	61.0		60.0	
Percentile				
25th	55.0		53.0	
75th	68.0		68.0	
Range	28.0-86.0		38.0-87.0	
Age group, years				
< 40	2	0.8	2	0.8
40-64	147	60.7	155	64.0
≥ 65	93	38.4	85	35.1
Race				
American Indian or Alaska Native	0	0.0	2	0.8
Asian	6	2.5	9	3.7
Black or African American	7	2.9	8	3.3
Native Hawaiian or other Pacific Islander	1	0.4	1	0.4
White	222	91.7	218	90.1
Not available	6	2.5	4	1.7
ECOG PS				
0	185	76.4	182	75.2
1	57	23.6	59	24.4
2	0	0.0	1	0.4
Primary site				
Fallopian tube	15	6.2	14	5.8
Ovarian	207	85.5	200	82.6
Primary peritoneal	20	8.3	28	11.6
Histology subtype				
Serous	202	83.5	189	78.1
Mucinous	1	0.4	3	1.2
Endometrioid	16	6.6	13	5.4
Transitional cell	2	0.8	2	0.8
Clear cell	6	2.5	9	3.7
Mixed	5	2.1	6	2.5
Other	10	4.1	20	8.3
Cytoreductive surgery for recurrent disease				
Yes	24	9.9	30	12.4
No	218	90.1	212	87.6
Time to recurrence since last platinum-based therapy, months				
6-12	102	42.1	100	41.3
> 12	140	57.9	142	58.7

Abbreviations: BV, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gemcitabine plus carboplatin; PL, placebo; SD, standard deviation.
*Randomly assigned patients.

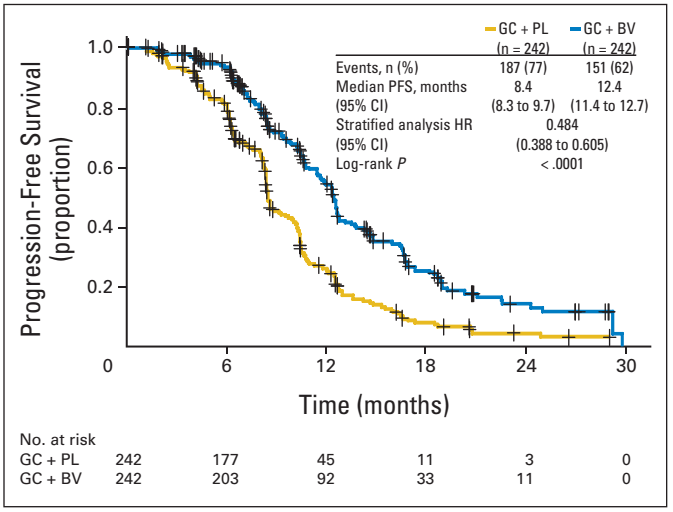

Fig 2. Kaplan-Meier estimates of progression-free survival (PFS) based on investigator assessment, censoring for non–protocol-specified therapy (randomly assigned patients). BV, bevacizumab; GC, gemcitabine plus carboplatin; HR, hazard ratio; PL, placebo.

Toxicity

Adverse events are summarized in Table 3. All patients in both arms experienced at least one adverse event. Serious adverse events occurred in 24.9% and 34.8% of patients in the PL and BV arms, respectively; grades 3 to 5 adverse events were reported in 82.4% and 89.5% of patients, respectively. Two deaths resulting from an adverse event were reported: one as a result of acute myocardial infarction (PL arm) and one as a result of intracranial hemorrhage in the context of newly diagnosed brain metastases (BV arm).

Grade 3 or higher hypertension (0.4% *v* 17.4%) and proteinuria (0.9% *v* 8.5%) occurred more frequently in the BV arm. The baseline incidence of hypertension in enrolled patients was similar between treatment groups (37.6% *v* 39.7% for PL and BV arms, respectively), but grade ≥ 3 hypertension was reported for one patient in the PL arm compared with 43 patients (17.4%) in the BV arm. Hypertension led to discontinuation of treatment in 3.6% of BV-treated patients. The development of proteinuria was closely monitored using urine protein-to-creatinine ratio measurements and tended to develop after more extended BV treatment; the median time to onset of grade ≥ 3 proteinuria was 26.5 months. Proteinuria led to discontinuation of BV treatment for 2.4% of patients. Three cases (1.2%) of reversible posterior leukoencephalopathy syndrome were reported in the BV arm; however, only two were confirmed by magnetic resonance imaging.

The rates of neutropenia and febrile neutropenia were similar in both arms. No GIPs occurred during study treatment or within the 30-day safety reporting period. Two GIPs occurred in the BV arm after study treatment discontinuation outside the 30-day safety reporting window, both at 69 days after the last BV dose. One patient, after 34 cycles of BV, had small bowel obstruction followed by a perforated gastric ulcer 69 days after study drug discontinuation by physician's decision. She underwent surgery for the GIP but did not receive poststudy anticancer therapy and died as a result of disease progression 82 days after onset of GIP. The second patient, after 39 cycles of BV, had an intestinal perforation after study drug discontinuation for PD (per RECIST) and receipt of one dose of pegylated liposomal doxorubicin. She underwent surgery and died as a result of disease progression 122 days after onset of GIP.

DISCUSSION

To our knowledge, OCEANS is the first positive, randomized, phase III trial evaluating the addition of a biologic therapy to a standard

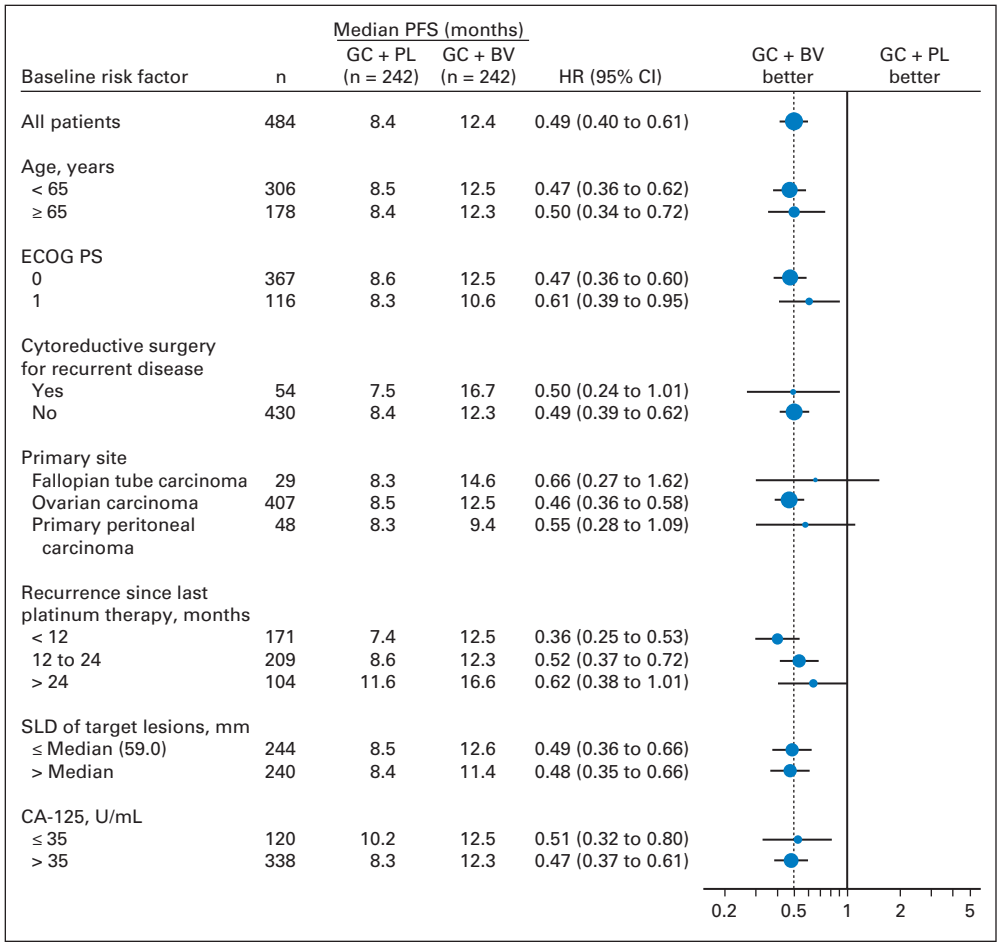

Fig 3. Progression-free survival (PFS) by baseline risk factor. Vertical dashed line indicates the hazard ratio (HR) for all patients. The diameter of a circle is proportional to the square root of the number of events. BV, bevacizumab; CA-125, cancer antigen 125; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gemcitabine plus carboplatin; PL, placebo; SLD, sum of longest diameters.

platinum doublet in ROC. The primary end point of investigator-assessed PFS was met, with an HR of 0.484 and a 4-month improvement in median PFS. In addition to the PFS benefit, there was a significant improvement in ORR and DOR. The primary analysis results were consistent across clinically relevant patient subgroups, and the formal prospective IRC-determined PFS analysis supports the investigator-assessed PFS and provides evidence that the PFS end point was reliably determined.

With respect to toxicity, no new safety concerns were observed in this patient population with ROC, and most importantly, there were no reports of GIPs during treatment. Two patients did experience GIPs 69 days after BV discontinuation. The additional toxicity that resulted from the use of BV with GC primarily consisted of a higher incidence of hypertension, proteinuria, and reversible posterior leukoencephalopathy syndrome.

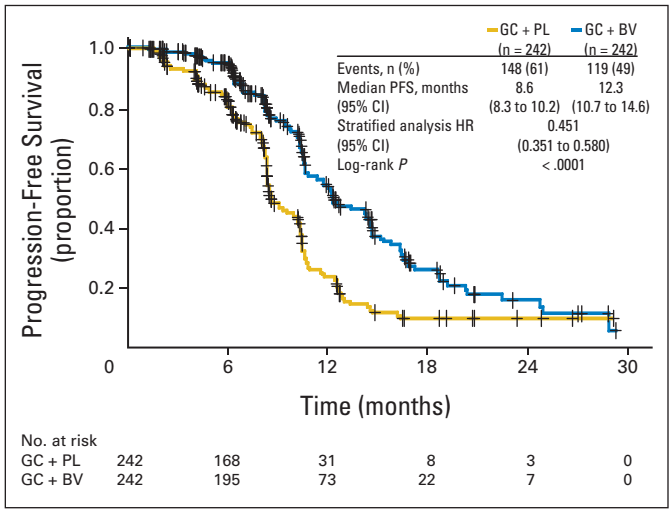

Fig 4. Kaplan-Meier estimates of progression-free survival (PFS) assessed by independent review committee, censoring for non–protocol-specified cancer therapy (randomly assigned patients). BV, bevacizumab; GC, gemcitabine plus carboplatin; HR, hazard ratio; PL, placebo.

Table 2. OS Results to Date

Result	First Interim OS Analysis* GC + PL (n = 242)	First Interim OS Analysis* GC + BV (n = 242)	Second Interim OS Analysis† GC + PL (n = 242)	Second Interim OS Analysis† GC + BV (n = 242)
Median OS, months	29.9	35.5	35.2	33.3
95% CI	26.4 to NE	30.0 to NE	29.9 to 40.3	29.8 to 35.5
HR	0.751		1.027	
95% CI	0.537 to 1.052		0.792 to 1.331	

Abbreviations: BV, bevacizumab; GC, gemcitabine plus carboplatin; NE, not estimable; OS, overall survival; PL, placebo.
*Data cutoff date: September 17, 2010.
†Data cutoff date: August 29, 2011.

Table 3. Safety Summary and Selected AEs*

Type of AE	GC + PL (n = 233)† No.	GC + PL (n = 233)† %	GC + BV (n = 247)‡ No.	GC + BV (n = 247)‡ %
Any	233	100.0	247	100.0
Grades 3 to 5	192	82.4	221	89.5
Grade 5	1	0.4	1	0.4
Serious	58	24.9	86	34.8
Grades 3 to 5	47	20.2	72	29.1
Leading to study drug (BV/PL) discontinuation	11	4.7	49	19.8
Special interest (any grade)	198	85.0	233	94.3
Arterial thromboembolic event (any grade)	2	0.9	7	2.8
Bleeding				
CNS (any grade)	1	0.4	2	0.8
Non-CNS (grade ≥ 3)	2	0.9	14	5.7
LV systolic dysfunction/CHF (grade ≥ 3)	2	0.9	3	1.2
Febrile neutropenia (any grade)	4	1.7	4	1.6
Fistula/abscess (any grade)§	1	0.4	4	1.6
GI perforation (any grade)	0	0.0	0	0.0
Hypertension (grade ≥ 3)	1	0.4	43	17.4
Neutropenia (grade ≥ 4)	51	21.9	51	20.6
Proteinuria (grade ≥ 3)	2	0.9	21	8.5
RPLS (any grade)	0	0.0	3	1.2‖
Wound-healing complication (grade ≥ 3)	0	0.0	2	0.8
Venous thromboembolic event (grade ≥ 3)	6	2.6	10	4.0

Abbreviations: AE, adverse event; BV, bevacizumab; CHF, congestive heart failure; GC, gemcitabine plus carboplatin; LV, left ventricular; PL, placebo; RPLS, reversible posterior leukoencephalopathy syndrome.

*Safety population. All safety analyses were based on the primary safety patient population, which was defined as all patients who received any partial or full dose of protocol treatment (G, C, BV, or PL). Only treatment-emergent AEs (ie, within 30 days after last dose of protocol treatment) were included in the safety analyses.

†Five patients randomly assigned to the GC + PL arm received one or two doses of BV in error and were assigned to the GC + BV arm for all safety analyses. Four patients randomly assigned to the GC + PL arm did not receive any protocol treatment and thus were not included in the safety analyses.

‡Five patients randomly assigned to the GC + PL arm received one or two doses of BV in error and were assigned to the GC + BV arm for all safety analyses.

§Includes all fistula/abscess events: anal fistula, female genital tract fistula, pelvic abscess, perirectal abscess, rectal abscess.

‖Two (0.8%) were cases of RPLS confirmed by magnetic resonance imaging.

As ovarian cancer becomes a chronic illness, treatments that prolong PFS, and therefore time without cytotoxic chemotherapy, become increasingly relevant. The latest Gynecologic Cancer Intergroup consensus conference on ovarian cancer concluded that PFS is a valid end point for the treatment of recurrent platinum-sensitive ovarian cancer.[17] The advantage of PFS as a primary end point is that it reflects tumor shrinkage and disease control of the study treatment.

The OS data from OCEANS are not yet mature, and the percentage of patients receiving subsequent therapy with chemotherapy and with BV or other antiangiogenic therapy is being observed for subsequent analysis. The National Comprehensive Cancer Network Compendium lists BV as a therapeutic option for ROC, making subsequent therapy with BV an available choice for many women with ROC in the United States.

Since completion of the ICON4 (International Collaborative Group for Ovarian Neoplasm-4), AGO-OVAR–NCIC CTG–EORTC, and Calypso trials, platinum-based doublets have gained acceptance as the best treatment in platinum-sensitive ROC.[4-6,18] The ICON4 and Calypso trials differ from OCEANS with respect to the inclusion of nonmeasurable and CA-125–evaluable disease, allowed length of cytotoxic chemotherapy, assessment modalities and intervals, and determination of progression. The data from OCEANS demonstrate that the addition of BV to GC can improve outcomes, and ongoing studies will assess whether this ability to add benefit is universal to other platinum-based combinations.

BV has also been evaluated in combination with standard paclitaxel plus C as part of initial therapy for women with ovarian cancer in two large, randomized phase III trials: ICON7 and GOG 218. Both of these trials met their primary end points and demonstrated an improvement in PFS.[19-22] Because of these results, in December 2011, the European Medicines Agency approved the use of BV in combination with paclitaxel plus C for the front-line treatment of advanced ovarian cancer in the European Union.[23]

The limitations of OCEANS include a lack of quality-of-life data and specimen collection for biomarker analysis. The strengths of OCEANS, however, lie in the robustness of the primary end point, with strict adherence to RECIST-defined progression and its supportive IRC analysis, and to the schedule of assessments. The median increase of 4 months in PFS is well above the frequency of radiologic reassessments (9 weeks).[24,25] The OCEANS data demonstrate that GC plus BV followed by BV until progression provides benefit over GC alone in ROC. OCEANS, GOG 218, and ICON7 represent three positive phase III trials of BV added to chemotherapy in the treatment of ovarian cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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