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Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial

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A B S T R A C T

Purpose
In platinum-resistant ovarian cancer (OC), single-agent chemotherapy is standard. Bevacizumab is active alone and in combination. AURELIA is the first randomized phase III trial to our knowledge combining bevacizumab with chemotherapy in platinum-resistant OC.

Patients and Methods
Eligible patients had measurable/assessable OC that had progressed < 6 months after completing platinum-based therapy. Patients with refractory disease, history of bowel obstruction, or > two prior anticancer regimens were ineligible. After investigators selected chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan), patients were randomly assigned to single-agent chemotherapy alone or with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks) until progression, unacceptable toxicity, or consent withdrawal. Crossover to single-agent bevacizumab was permitted after progression with chemotherapy alone. The primary end point was progression-free survival (PFS) by RECIST. Secondary end points included objective response rate (ORR), overall survival (OS), safety, and patient-reported outcomes.

Results
The PFS hazard ratio (HR) after PFS events in 301 of 361 patients was 0.48 (95% CI, 0.38 to 0.60; unstratified log-rank $P < .001$). Median PFS was 3.4 months with chemotherapy alone versus 6.7 months with bevacizumab-containing therapy. RECIST ORR was 11.8% versus 27.3%, respectively ($P = .001$). The OS HR was 0.85 (95% CI, 0.66 to 1.08; $P < .174$; median OS, 13.3 v 16.6 months, respectively). Grade $\geq$ 2 hypertension and proteinuria were more common with bevacizumab. GI perforation occurred in 2.2% of bevacizumab-treated patients.

Conclusion
Adding bevacizumab to chemotherapy statistically significantly improved PFS and ORR; the OS trend was not significant. No new safety signals were observed.

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INTRODUCTION

Platinum-free interval is a strong predictor of treatment success in recurrent ovarian cancer.[1] Patients whose disease relapses within 6 months after platinum-containing therapy are categorized as having platinum-resistant disease. At first relapse, approximately 25% of patients have platinum-resistant ovarian cancer; almost all patients with recurrent disease ultimately develop platinum resistance.

In the platinum-resistant setting, the most active single agents are pegylated liposomal doxorubicin (PLD), paclitaxel, and topotecan.[2-6] Several trials in this setting have shown that combining chemotherapy agents increases toxicity without improving efficacy.[2,7,8] Thus, the outlook for patients remains poor; median overall survival (OS) is approximately 12 months,[9] and novel strategies are needed.

A new approach is to combine single-agent chemotherapy with biologic therapies. The monoclonal antibody bevacizumab, which targets all isoforms of vascular endothelial growth factor (VEGF)–A, is active in platinum-resistant ovarian cancer, both as monotherapy[10,11] and combined with chemotherapy.[12,13] AURELIA (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) is

the first randomized trial to our knowledge evaluating the combination of bevacizumab and chemotherapy in platinum-resistant recurrent ovarian cancer. Strict exclusion criteria were implemented to reduce the risk of GI perforation, which was previously reported at a high incidence in patients receiving bevacizumab for heavily pretreated ovarian cancer.[11] We report the efficacy and safety results from AURELIA. Patient-reported outcomes are reported in an accompanying article.[14]

PATIENTS AND METHODS

Study Design

The open-label randomized phase III AURELIA trial was designed to determine the impact on efficacy, safety, and quality of life (QoL) of combining bevacizumab with chemotherapy for platinum-resistant recurrent ovarian cancer. The primary end point was investigator-assessed progression-free survival (PFS) by RECIST, defined as the interval between random assignment and first radiologically documented disease progression or death, whichever occurs first (Appendix, online only). Secondary end points included objective response rate (ORR) according to RECIST (version 1.0) and/or Gynecologic Cancer Intergroup (GCIG) cancer antigen (CA) −125 criteria, OS, safety, tolerability, and QoL. Three separate analyses of ORR were prespecified: RECIST alone, GCIG CA-125 response criteria alone, and both criteria combined.

Patient Population

Eligible patients had histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer (measurable by RECIST [version 1.0] or assessable by GCIG CA-125 response criteria) that had progressed within 6 months of completing ≥ four cycles of platinum-based therapy. Inclusion criteria included: age ≥ 18 years, Eastern Cooperative Oncology Group performance status ≤ 2, and adequate liver, renal, and bone marrow function. Patients who had received > two prior anticancer regimens

or who had refractory disease (progression during previous platinum-containing therapy) were ineligible, as were patients with a history of bowel obstruction (including subocclusive disease) related to underlying disease, a history of abdominal fistula, GI perforation, or intra-abdominal abscess, or evidence of rectosigmoid involvement by pelvic examination, bowel involvement on computed tomography, or clinical symptoms of bowel obstruction. Additional exclusion criteria included: prior radiotherapy to the pelvis or abdomen, surgery (including open biopsy) within 4 weeks before starting study therapy (within 24 hours for minor surgical procedures) or anticipated need for major surgery during study treatment, current or recent treatment with another investigational drug within 30 days before first study dose, untreated CNS disease or symptomatic CNS metastasis, history or evidence of thrombotic or hemorrhagic disorders within 6 months before first study treatment, uncontrolled hypertension or active clinically significant cardiovascular disease, or nonhealing wound, ulcer, or bone fracture.

All patients provided written informed consent before undergoing any study-specific procedures. The study was conducted in accordance with the principles of the Declaration of Helsinki and local laws and regulations of each participating country and conformed to the principles outlined in the Good Clinical Practice International Conference on Harmonisation Tripartite Guideline and the EU Clinical Trial Directive if applicable. The protocol was approved by national and/or participating-institution independent ethics committees.

Treatment

Investigators selected single-agent chemotherapy on an individual patient basis from the following options, with appropriate premedication according to local standards: paclitaxel 80 mg/m^2 intravenously (IV) on days 1, 8, 15, and 22 every 4 weeks; PLD 40 mg/m^2 IV on day 1 every 4 weeks; or topotecan 4 mg/m^2 IV on days 1, 8, and 15 every 4 weeks or 1.25 mg/m^2 on days 1 to 5 every 3 weeks. Patients were then randomly assigned to receive the selected chemotherapy either alone (CT) or with bevacizumab 10 mg/kg every 2 weeks (or 15 mg/kg every 3 weeks in patients receiving topotecan in a schedule repeated every 3 weeks; BEV-CT). Patients were stratified according
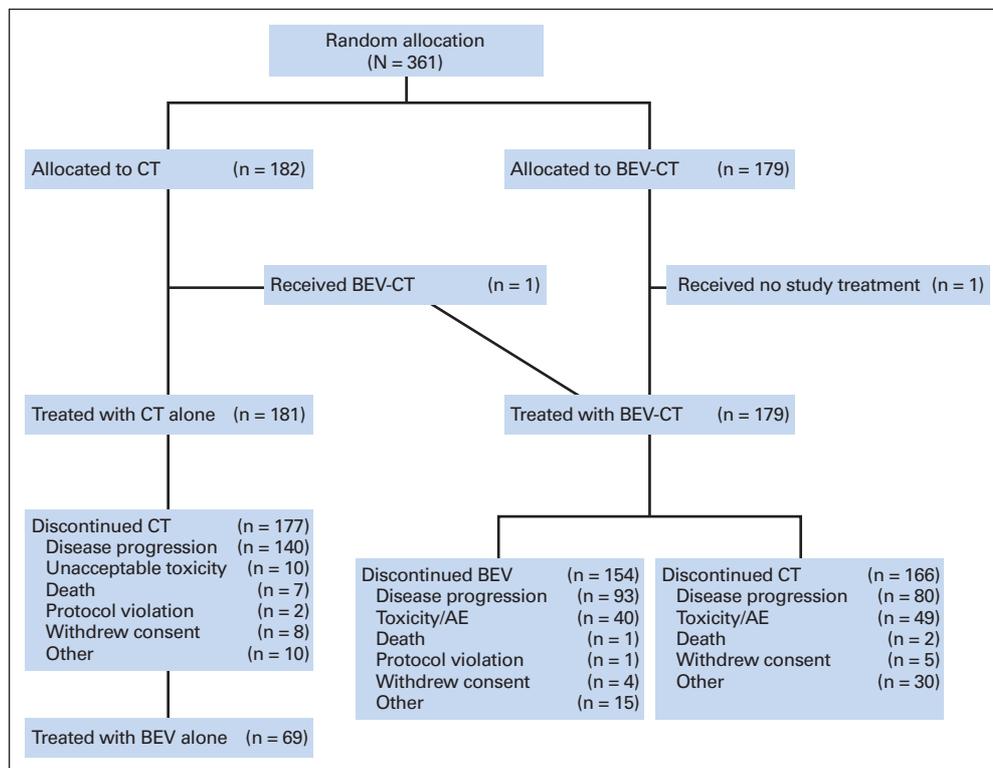
Fig 1. Patient disposition. AE, adverse event; BEV, bevacizumab; CT, chemotherapy.

to selected chemotherapy (PLD *v* paclitaxel *v* topotecan), prior antiangiogenic therapy (yes *v* no), and platinum-free interval (< 3 *v* 3 to 6 months from last platinum therapy to subsequent progression). Chemotherapy and bevacizumab were continued until disease progression, unacceptable toxicity, or consent withdrawal. Patients in the BEV-CT arm experiencing toxicity necessitating discontinuation of one agent could continue the nonimplicated agent as monotherapy. Bevacizumab dose reduction was not permitted. Chemotherapy dose modification guidelines were consistent with standard clinical practice. Patients randomly assigned to CT could cross over to single-agent bevacizumab 15 mg/kg once every 3 weeks on clear evidence of progression after careful risk-benefit assessment for each patient by the investigator. Patients in the BEV-CT arm received standard-of-care treatment (without bevacizumab) at progression. Bevacizumab was discontinued in patients with any grade of GI perforation. The Independent Data Monitoring Committee (IDMC) reviewed safety data on an ongoing basis. Recruitment to each individual chemotherapy cohort was closed after 120 patients were enrolled.

Study Assessments

Tumor assessment was performed at baseline and repeated every 8 weeks (or every 9 weeks in patients receiving topotecan in a schedule repeated every 3 weeks), using the same assessment technique (preferably by computed tomography or magnetic resonance imaging in case of contrast allergy) throughout the study. Responses were confirmed by computed tomography scan at least 4 weeks after the first response. Patients were observed for survival for ≥ 12 months. Safety was assessed before each cycle and within 30 days of completing treatment. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical Design and Analysis

Initially, a sample size of 300 patients was planned, calculated so that 228 PFS events would provide 80% power with a one-sided log-rank test at $\alpha = 0.05$, assuming a hazard ratio (HR) of 0.72, corresponding to median PFS of 4.0 months with CT versus 5.56 months with BEV-CT. The protocol was amended, increasing the sample size to 332 patients, providing 80% power to detect a PFS HR of 0.70 with two-sided log-rank testing at $\alpha = 0.05$ after 247 PFS events, assuming a median PFS of 4.0 months with CT and 5.7 months with BEV-CT. At the recommendation of the IDMC, the sample size was increased further to ≥ 360 patients, with primary analysis planned after 290 PFS events based on an HR of 0.72 and 80% power. The recommendation of the IDMC in January 2011 followed review of the PFS event rate in the CT arm only (without preliminary review of treatment effect) and the overall treatment discontinuation rate.

PFS in the two treatment arms was compared using an unstratified two-sided log-rank test. A post hoc analysis using a stratified two-sided log-rank test was also performed. Final OS analysis was performed after deaths in 70% of patients.

Efficacy analyses were based on the intent-to-treat population (all randomly assigned patients); safety analyses were based on the safety population (all patients who received ≥ one dose of study treatment; adverse events occurring in the CT arm after patients had switched to bevacizumab monotherapy were excluded). Exploratory analyses of safety and efficacy were prespecified for the subgroup of patients with ascites at baseline. Post hoc analyses were undertaken to determine the proportion of patients undergoing paracentesis during study therapy. No interim efficacy analyses were preplanned (to ensure sufficient sample sizes in each chemotherapy cohort allowing corresponding exploratory assessment with each chemotherapy combination regimen, given anticipated imbalances in accrual rate between chemotherapy cohorts). The IDMC reviewed safety on an ongoing basis using real-time information, and thus, no interim safety analyses were planned.

RESULTS

Patient Population

Between October 2009 and April 2011, 361 patients were enrolled. Investigator selection of chemotherapy was evenly distributed

among the three options (PLD, n = 126; paclitaxel, n = 115; topotecan, n = 120), as expected because of the capping of the cohorts. The first cohort to be fully recruited was PLD (October 2010); recruitment to the paclitaxel and topotecan cohorts was completed in April 2011.

Patient disposition is shown in Figure 1. Baseline characteristics are summarized in Table 1.

Efficacy

The data cutoff date for the primary analysis was November 14, 2011. Median duration of follow-up was 13.9 months in the CT arm versus 13.0 months in the BEV-CT arm.
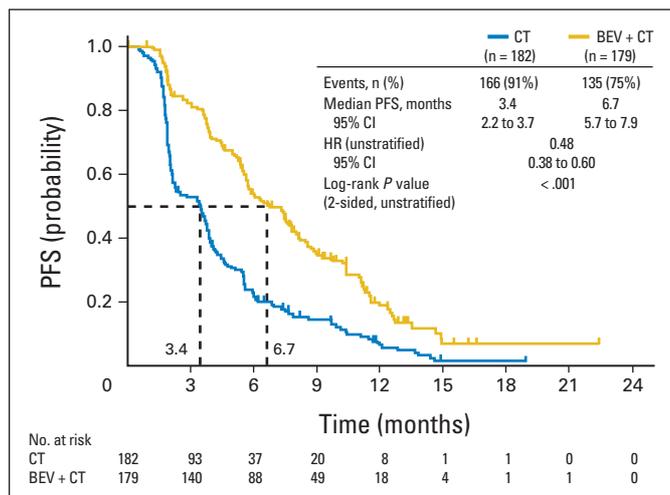
The study met its primary objective, demonstrating a significant improvement in PFS with the addition of bevacizumab to chemotherapy (two-sided unstratified log-rank test $P < .001$; HR, 0.48; 95% CI, 0.38 to 0.60; Fig 2). Median PFS was 3.4 months (95% CI, 2.2 to 3.7) with CT versus 6.7 months (95% CI, 5.7 to 7.9 months) with BEV-CT. This finding was supported by the stratified analysis (two-sided stratified log-rank test $P < .001$; HR, 0.42; 95% CI, 0.32 to 0.53). The PFS benefit was seen consistently across all subgroups evaluated (Appendix Fig A1, online only).

Response was evaluable by RECIST and/or GCIG CA-125 criteria in 350 patients. The ORR was 12.6% with CT versus 30.9% with BEV-CT (18.3 percentage-point difference [95% CI, 9.6 to 27.0]; two-sided χ^2 with Schouten correction $P < .001$). In the 287 patients

Table 1. Baseline Patient Characteristics				
	Chemotherapy Alone (n = 182)		Bevacizumab Plus Chemotherapy (n = 179)	
Characteristic	No.	%	No.	%
Age, years				
Median	61		62	
Range	25-84		25-80	
Origin of cancer, ovary	157	86	167	93
Histology at diagnosis				
Serous/adenocarcinoma	152	84	156	87
Endometrioid	9	5	8	5
Clear cell	12	7	4	2
Histologic grade at diagnosis				
1	9	5	10	6
2	48	26	53	30
3	105	58	94	53
Missing	20	11	22	12
Prior antiangiogenic therapy*	14	8	12	7
Two prior chemotherapy regimens	78	43	72	40
Platinum-free interval < 3 months*†	46	25	50	28
ECOG performance status				
0	99	54	107	60
1	69	38	58	32
2	11	6	12	7
Missing	3	2	2	1
Measurable disease	144	79	143	80
Ascites	54	30	59	33

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Stratification factor.
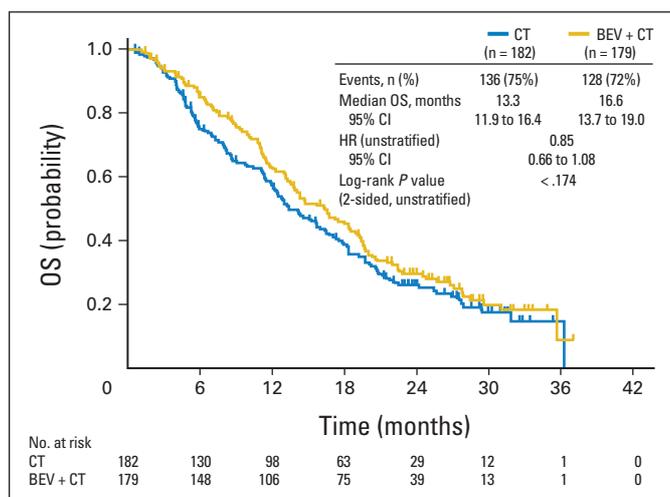†From last platinum to subsequent disease progression.

Fig 2. Progression-free survival (PFS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.

Fig 4. Summary of treatment exposure. One cycle was 4 weeks long, except for topotecan, which could be administered on days 1 to 5 every 3 weeks. BEV, bevacizumab; CT, chemotherapy.

with responses evaluable by RECIST, the ORR was 11.8% versus 27.3% for CT and BEV-CT, respectively ($P = .001$). The ORR according to GCIG CA-125 criteria alone (n = 297) was 11.6% with CT versus 31.8% with BEV-CT ($P < .001$), indicating a consistent ORR benefit irrespective of the assessment method used.
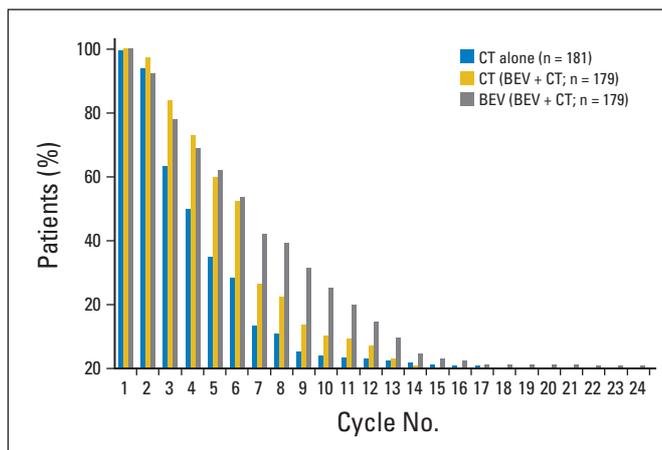
Data cutoff for the final OS analysis was January 25, 2013. There was no statistically significant difference in OS between the regimens (HR, 0.85; 95% CI 0.66 to 1.08; unstratified log-rank $P < .174$). Median OS was 13.3 months (95% CI, 11.9 to 16.4) with CT versus 16.6 months (95% CI, 13.7 to 19.0) with BEV-CT (Fig 3).

Treatment Exposure

The median duration of therapy was three cycles (range, one to 17 cycles) in the CT arm versus six cycles (range, one to 24 cycles) in the BEV-CT arm. Chemotherapy exposure was markedly higher in the BEV-CT arm, reflecting the substantially longer PFS in bevacizumab-treated patients (Fig 4). At the time of data cutoff for the

Fig 3. Overall survival (OS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.

final OS analysis, 72 patients (40%) in the CT arm had received single-agent bevacizumab after progression on CT alone.

Safety

The safety population included 360 patients. One patient randomly assigned to CT also received bevacizumab and was therefore included in the BEV-CT safety population. One patient randomly assigned to BEV-CT received no study drug so was excluded from the safety population.

Adverse events of special interest (reported in previous bevacizumab clinical trials) occurred in 40.3% of the CT arm versus 57.0% of the BEV-CT arm. There was an increased incidence of grade ≥ 2 hypertension and proteinuria with bevacizumab (Table 2). Grade ≥ 2 GI perforation was observed in four patients (2.2%) receiving BEV-CT (grade ≥ 3, 1.7%) and none of those receiving CT alone. There was no excess of other adverse events of special interest.

Other grade ≥ 3 adverse events are summarized in Figure 5. Grade ≥ 3 hematologic toxicity occurred at a similar incidence in the two treatment arms. Adverse events possibly related to tumor burden, such as severe abdominal pain, vomiting, fatigue, and dyspnea, were less common with BEV-CT. However, hand-foot syndrome and peripheral sensory neuropathy were more common with BEV-CT. Because these effects are characteristic cumulative toxicities of PLD and paclitaxel, respectively, and may be related to the increased chemotherapy exposure in the BEV-CT arm, additional exploratory analyses were undertaken. Results suggest a similar time course for these cumulative toxicities in the two arms (Appendix Fig A2, online only). When considering only patients at risk (ie, those still receiving study therapy), the proportion of patients experiencing these adverse events within each cycle was similar in the two arms.

During the study period, there were five deaths (2.8% of patients) in each arm that were not considered to be caused primarily by progressive disease. In the CT arm, there was one case each of death resulting from infection with neutropenia, cardiac failure, septic shock, peritonitis, and GI hemorrhage; the patient with GI hemorrhage had already experienced disease progression while receiving CT and had switched to single-agent bevacizumab. In the BEV-CT arm, there was one case each of death resulting from infection with neutropenia, GI hemorrhage, GI perforation, cardiac arrest, and shock.

Table 2. Summary of Grade ≥ 3 (and selected grade ≥ 2) AEs of Special Interest				
	Chemotherapy Alone (n = 181)		Bevacizumab Plus Chemotherapy (n = 179)	
AE	No.	%	No.	%
Hypertension	2	1	13	7
Grade ≥ 2	12	7	36	20
Proteinuria	0	0	3	2
GI perforation	0	0	3	2
Grade ≥ 2	0	0	4	2
Fistula/abscess	0	0	2	1
Grade ≥ 2	0	0	4	2
Bleeding	2	1	2	1
Thromboembolic event	8	4	9	5
Arterial	0	0	4	2
Venous	8	4	5	3
Wound-healing complication	0	0	0	0
Reversible posterior leukoencephalopathy syndrome	0	0	1	1
Congestive heart failure	1	1	1	1
Cardiac disorders (excluding congestive heart failure)	0	0	0	0

Abbreviation: AE, adverse event.

Subgroup With Ascites at Baseline

In the subgroup of 113 patients (31% of the randomly assigned population) with ascites at baseline, nine of the patients (17%) treated with CT alone underwent paracentesis after starting study treatment, compared with one patient (2%) receiving BEV-CT (on day of first bevacizumab administration) during the treatment period (Appendix Fig A3, online only).

DISCUSSION

The AURELIA trial met its primary objective, demonstrating statistically significant improvement in PFS (HR, 0.48; 95% CI, 0.38 to 0.60)
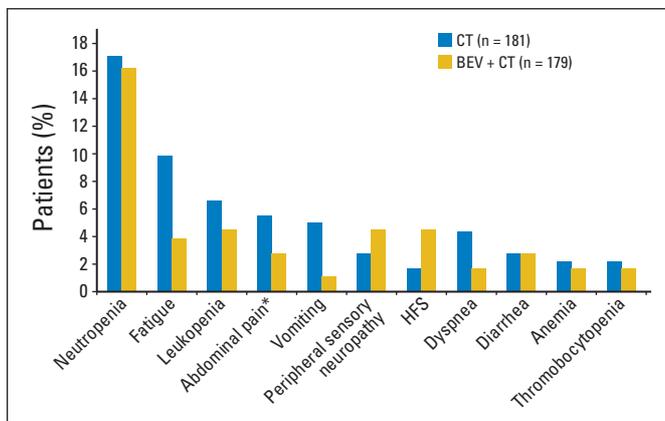
Fig 5. Other grade ≥ 3 adverse events (Medical Dictionary for Regulatory Activities–preferred terms). BEV, bevacizumab; CT, chemotherapy; HFS, hand-foot syndrome. (*) Includes upper abdominal pain.

with the addition of bevacizumab to chemotherapy for platinum-resistant ovarian cancer. To our knowledge, AURELIA is the first randomized phase III trial to demonstrate a PFS benefit with combination therapy over single-agent chemotherapy and a benefit of biologic therapy in this setting.

PFS benefit was seen consistently across all subgroups reported. The improvement in the subgroup of patients with ascites, who have a poor prognosis, is noteworthy. Although the PFS HR does not suggest a more pronounced PFS benefit in patients with versus without ascites at baseline, the absence of paracentesis after the first bevacizumab dose suggests that adding bevacizumab to chemotherapy improved control of ascites. Preclinical research indicates that tumor VEGF secretion is at least partially responsible for the development and maintenance of ascites,[15] which may explain the control of ascites observed with bevacizumab therapy.

No statistically significant difference was observed in OS (secondary end point). However, the trial was not designed to detect an OS difference, because crossover to bevacizumab was permitted from the CT arm and occurred in 40% of patients initially randomly assigned to CT.

The AURELIA results add to findings from three previously reported randomized phase III trials of patients earlier in their treatment course. Bevacizumab combined with chemotherapy and continued as a single agent significantly improved PFS compared with chemotherapy alone in the first-line setting (GOG-0218 [Gynecologic Oncology Group] and ICON7 [International Collaboration on Ovarian Neoplasms])[16,17] and the platinum-sensitive recurrent setting (OCEANS [Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Antiangiogenic Therapy in Platinum-Sensitive Recurrent Disease]).[18] Taken together, these data provide robust evidence for the role of bevacizumab in ovarian cancer treatment. However, its activity in patients whose disease relapses after first-line bevacizumab-containing therapy is still unknown. In colorectal cancer, continuing bevacizumab with second-line chemotherapy significantly improved OS (primary end point) in patients who had received first-line bevacizumab-containing regimens.[19] In AURELIA, only 26 patients (7%) had received prior antiangiogenic therapy; thus, no conclusions could be drawn on the efficacy of bevacizumab in bevacizumab-pretreated patients. However, studies in ovarian cancer addressing this issue are ongoing.

The efficacy of bevacizumab-containing therapy compares favorably with other treatments in this setting. Chemotherapy doublets have not improved efficacy over single-agent chemotherapy.[2,7,8] Ongoing phase III trials evaluating targeted therapies in recurrent disease include TRINOVA-1 (Trebananib in Ovarian Cancer), which showed improved PFS (HR, 0.66) with the addition of trebananib to weekly paclitaxel in platinum-resistant or intermediate-sensitive disease,[20] and PROCEED (Platinum-Resistant Ovarian Cancer Evaluating EC145 in Combination With Doxil), evaluating vintafolide added to PLD in platinum-resistant disease.[21]

The open-label design of AURELIA may be criticized for potential bias, especially because PFS was determined by investigators. The optional crossover from chemotherapy alone to bevacizumab at progression was considered important when designing the trial, because the single-agent efficacy of bevacizumab was already established. However, a drawback of this ethically understandable permitted crossover was the further reduced ability to detect an OS difference,

which has become increasingly important, particularly to some regulatory authorities.

Another potential criticism of the trial design is the lack of a third bevacizumab-alone arm, avoiding the toxicity of chemotherapy. The efficacy of single-agent bevacizumab has been shown in single-arm phase II studies in the recurrent ovarian cancer setting,[10,11] but AURELIA provides no insight into the efficacy of BEV-CT versus bevacizumab alone.

The 2.2% incidence of GI perforation with BEV-CT (grade $\geq$ 3, 1.7%) is lower than that reported by Cannistra et al[11] in heavily pretreated patients. Simpkins et al[22] observed no GI perforations with bevacizumab therapy in heavily pretreated platinum-resistant disease after implementing a patient-screening program to exclude patients with clinical symptoms of bowel obstruction, evidence of rectosigmoid involvement, or bowel involvement on computed tomography. Additional retrospective studies have identified bowel obstruction and rectovaginal involvement as potential risk factors for GI perforation.[23,24] AURELIA had strict exclusion criteria to ensure that patients at increased risk of GI perforation were not enrolled. It seems that this approach was effective in limiting the incidence of GI perforation in AURELIA. Further study is required before the tolerability observed in AURELIA can be extrapolated to later lines. In heavily pretreated patients, well-defined radiologic criteria may enable identification of those most at risk of GI perforation.

Consistent with the safety profile of bevacizumab-containing therapy in previously reported trials in ovarian cancer and other tumor types, grade $\geq$ 2 hypertension and proteinuria were more common with bevacizumab than with chemotherapy alone. However, there were no new safety signals. When analyzed per cycle, the proportions of patients experiencing peripheral neuropathy or hand-foot syndrome were similar in the two treatment arms. Therefore, the higher cumulative incidence of these two adverse events in the bevacizumab-containing arm may be attributable to the longer PFS—and thus longer chemotherapy exposure—in patients benefitting from bevacizumab rather than bevacizumab-related exacerbation of chemotherapy toxicity.

In summary, AURELIA is the first trial to our knowledge demonstrating a significant PFS benefit of either a combination regimen or a biologic agent in platinum-resistant ovarian cancer. On the basis of the statistically significantly improved PFS, together with response rate and safety results, bevacizumab combined with chemotherapy

should be considered a standard option in platinum-resistant ovarian cancer.

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Appendix

Definition of Progression

For patients with measurable disease at random assignment, progression is defined as any of the following:

- At least a 20% increase in the sum of longest-diameter (LD) target lesions, taking as reference the smallest sum LD recorded since study entry
- In the case where the only target lesion is a solitary pelvic mass measured by physical examination that is not radiographically measurable, a 50% increase in LD is required, taking as reference the smallest LD recorded since study entry
- The appearance of ≥ one new lesion
- Death resulting from disease without prior objective documentation of progression
- Unequivocal progression of existing nontarget lesions, other than pleural effusions without cytologic proof of neoplastic origin, in the opinion of the treating physician (in this circumstance, explanation must be provided)

For patients with nonmeasurable disease at random assignment, progression is defined as any of the following:

- The appearance of ≥ one new measurable lesion
- Unequivocal progression of existing nontarget lesions, other than pleural effusions without cytologic proof of neoplastic origin, in the opinion of the treating physician (in this circumstance, explanation must be provided)
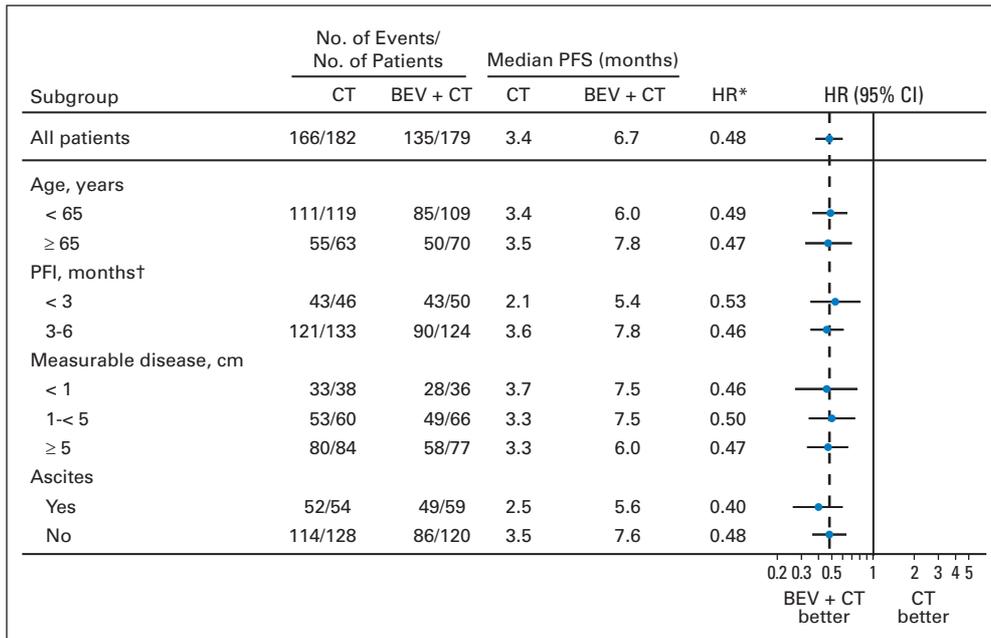- Death resulting from disease without prior objective documentation of progression

Of note, the protocol specified that the following patients (with measurable or nonmeasurable disease) should also be defined as experiencing progression:

- Global deterioration in health status attributable to the disease, requiring a change in therapy without objective evidence of progression. Patients should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression even after discontinuation of treatment.

However, before database lock, it was agreed and specified in the statistical analysis plan that for the core progression-free survival analysis, such patients should not be counted as having progressive disease, either as an event or as a censoring point. The intention was to keep a definition as close as possible to RECIST. Nevertheless, two sensitivity analyses were performed to determine the effect of using symptomatic deterioration as an event or censoring point. In the intent-to-treat population, eight patients treated with chemotherapy alone and 12 patients treated with bevacizumab in combination with chemotherapy experienced progression defined by symptomatic deterioration alone. The sensitivity analyses showed hazard ratios (HRs) almost identical to the core analysis HR of 0.48 (95% CI, 0.38 to 0.60). When the 20 patients with progressive disease defined by symptomatic deterioration alone were counted as events, the HR was 0.48 (95% CI, 0.38 to 0.61). When considered as a censoring point, the HR was 0.47 (95% CI, 0.37 to 0.59).

Subgroup	No. of Events/ No. of Patients		Median PFS (months)		HR*	HR (95% CI)
	CT	BEV + CT	CT	BEV + CT		
All patients	166/182	135/179	3.4	6.7	0.48	
Age, years						
< 65	111/119	85/109	3.4	6.0	0.49	
≥ 65	55/63	50/70	3.5	7.8	0.47	
PFI, months†						
< 3	43/46	43/50	2.1	5.4	0.53	
3-6	121/133	90/124	3.6	7.8	0.46	
Measurable disease, cm						
< 1	33/38	28/36	3.7	7.5	0.46	
1-< 5	53/60	49/66	3.3	7.5	0.50	
≥ 5	80/84	58/77	3.3	6.0	0.47	
Ascites						
Yes	52/54	49/59	2.5	5.6	0.40	
No	114/128	86/120	3.5	7.6	0.48	

0.2 0.3 0.5   1   2 3 4 5

BEV + CT better   CT better

Fig A1. Subgroup analysis of progression-free survival (PFS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio; PFI, platinum-free interval. (*) Unstratified HR. (†) Missing in eight patients.
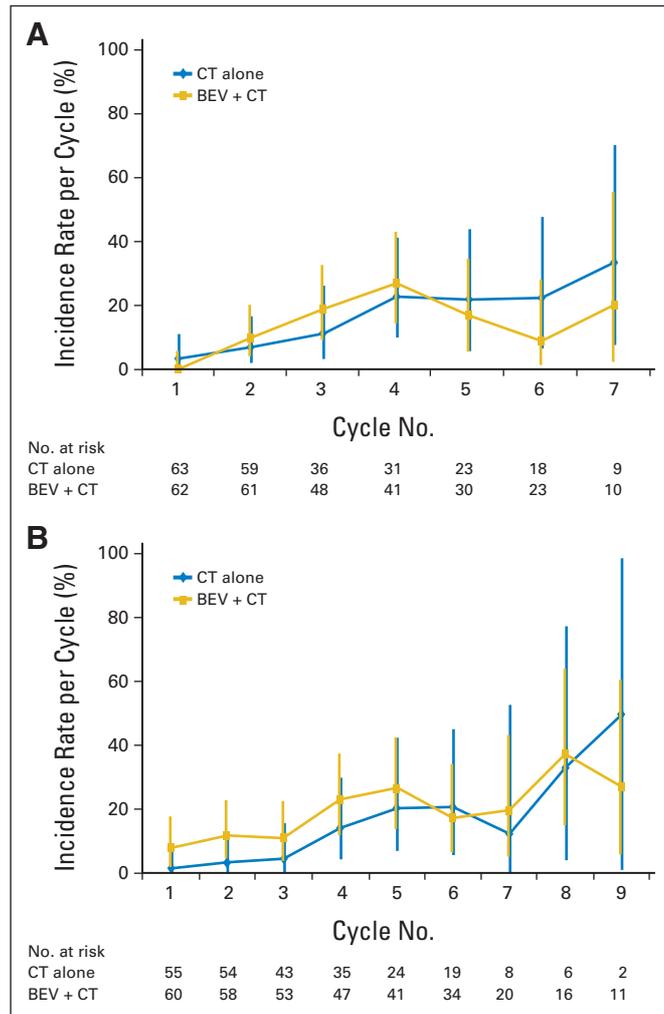
Fig A2. Time course of cumulative chemotherapy-related grade ≥ 2 adverse events. Grade ≥ 2 (A) hand-foot syndrome (pegylated liposomal doxorubicin [PLD] cohort) and (B) peripheral sensory neuropathy (paclitaxel cohort) by cycle. Incidence based on number at risk receiving (A) PLD or (B) paclitaxel in respective cycle. Vertical bars represent 95% Pearson-Clopper CIs. Cycles with < 10 patients in each arm not shown. BEV, bevacizumab; CT, chemotherapy.
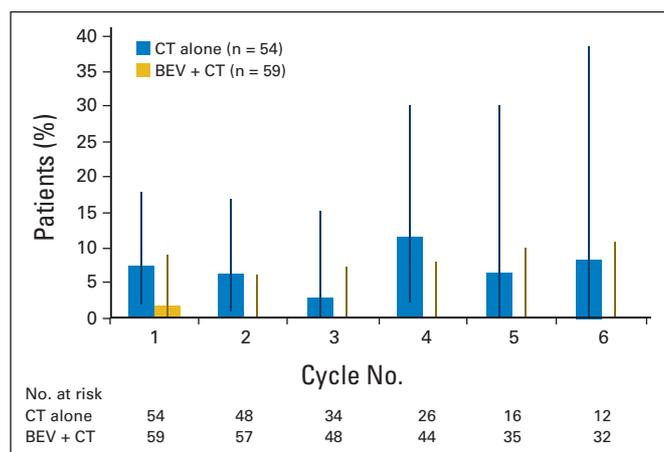
Fig A3. Incidence of paracentesis by cycle and treatment arm. Data not shown for cycles with < 10 patients in one or both arms. Vertical bars represent 95% exact CIs. BEV, bevacizumab; CT, chemotherapy.