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CORRESPONDENCE

Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial

TO THE EDITOR: In a previous issue of *Journal of Clinical Oncology*, we reported results from the open-label, randomized phase III AURELIA (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) trial demonstrating that combining bevacizumab with single-agent chemotherapy for treatment of platinum-resistant recurrent ovarian cancer (PROC) significantly improved progression-free survival (PFS), the primary end point, as well as the objective response rate (ORR) and the patient-reported outcome end point of abdominal/GI symptoms in the intent-to-treat population of 361 patients.[1,2] We observed no significant difference in overall survival (OS) between treatment arms, though the trial was not designed for us to formally compare OS. In addition, the extensive cross-over of 40% of patients to bevacizumab from chemotherapy alone complicated interpretation.

In AURELIA, investigators chose their preferred chemotherapy (from weekly paclitaxel, pegylated liposomal doxorubicin [PLD], or topotecan) for each patient before randomization. Enrollment onto each cohort was capped to enable meaningful evaluation of each regimen. Patients were stratified by selected chemotherapy but not randomly assigned among chemotherapy regimens. In all three chemotherapy cohorts, PFS was significantly improved by adding bevacizumab to chemotherapy, consistent with the overall results. PFS hazard ratios (HRs) were 0.46 (95% confidence interval [95% CI], 0.30 to 0.71) in the paclitaxel cohort (median, 10.4 *v* 3.9 months; Fig 1A), 0.57 (95% CI, 0.39 to 0.83) for PLD (median 5.4 *v* 3.5 months favoring bevacizumab-containing therapy), and 0.32 (95% CI, 0.21 to 0.49) for topotecan (median 5.8 *v* 2.1 months, respectively).

ORR by RECIST was higher with bevacizumab-containing therapy versus chemotherapy alone in the paclitaxel cohort (53.3% *v* 30.2%, respectively; difference, 23.1%; 95% CI, 1.7% to 44.5%) and the topotecan cohort (17.0% *v* 0.0%; difference, 17.0%; 95% CI, 5.1% to 28.9%), with a less pronounced effect in the PLD cohort (13.7% *v* 7.8%; difference, 5.9%; 95% CI, −7.2% to 19.0%).

Analyses of patient-reported outcomes were based on a responder analysis approach to compare the proportion of patients in each treatment arm achieving ≥ 15% improvement at week 8 or 9 in an abdominal/GI symptom subscale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire OV28. In each cohort, numerically more patients receiving bevacizumab-containing therapy than chemotherapy alone achieved ≥ 15% improvement in abdominal/GI symptoms. The proportions were 25.0% versus 13.0%, respectively, in the paclitaxel cohort (difference, 12.0%; 95% CI, −4.9% to 28.9%), 20.0% versus 8.8% in the topotecan cohort (difference, 11.2%; 95% CI, −3.2% to 25.7%) and 21.1% versus 6.8% in the PLD cohort (difference, 14.3%; 95% CI, 0.9% to 27.6%).

We found no significant difference in OS between treatment arms in any of the chemotherapy cohorts; this was consistent with the overall population. Unadjusted HRs were 0.91 (95% CI, 0.62 to 1.36) for PLD (median, 13.7 months with bevacizumab-containing therapy

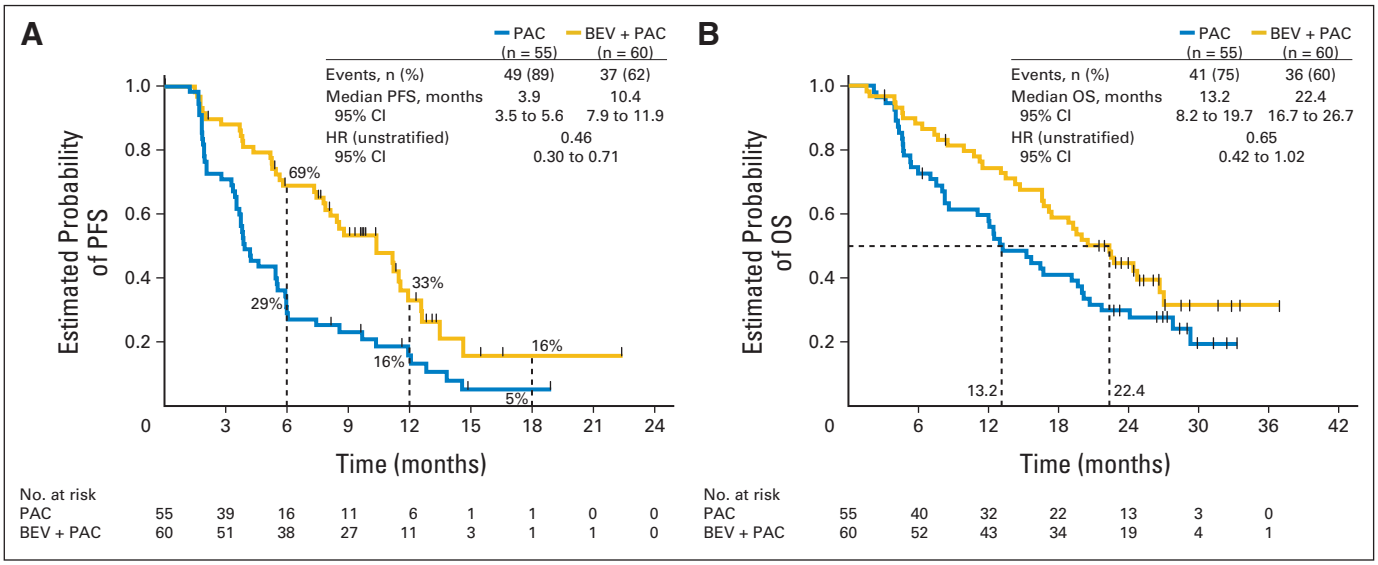

Fig 1. Weekly paclitaxel (PAC) cohort. (A) Progression-free survival (PFS) with a data cutoff date of November 14, 2011. (B) Overall survival (OS) with a data cutoff date of January 25, 2013. BEV, bevacizumab; HR, hazard ratio.

Table 1. Distribution of Baseline Characteristics and Identified Prognostic Factors

Characteristic	PLD		Topotecan		Weekly Paclitaxel	
	No Bevacizumab (n = 64)	Bevacizumab (n = 62)	No Bevacizumab (n = 63)	Bevacizumab (n = 57)	No Bevacizumab (n = 55)	Bevacizumab (n = 60)
Recruitment	October 2009-October 2010		October 2009-April 2011		October 2009-April 2011	
Age, years						
Median (range)	62 (32-77)	63.5 (39-78)	61 (35-84)	60 (26-80)	60 (25-80)	60 (25-79)
Histology at diagnosis*						
Serous or adenocarcinoma	49 (77)	53 (85)	55 (87)	50 (88)	48 (87)	53 (88)
Clear cell	6 (9)	1 (2)	3 (5)	1 (2)	3 (5)	2 (3)
FIGO stage III or IV	52 (81)	56 (90)	56 (89)	55 (96)	48 (87)	54 (90)
Histologic grade at diagnosis						
1	4 (6)	1 (2)	2 (3)	2 (4)	3 (5)	7 (12)
2	14 (22)	15 (24)	17 (27)	20 (35)	17 (31)	18 (30)
3	40 (63)	36 (58)	40 (63)	27 (47)	25 (45)	31 (52)
Missing	6 (9)	10 (16)	4 (6)	8 (14)	10 (18)	4 (7)
Two previous chemotherapy regimens	21 (33)	16 (26)	29 (46)	23 (40)	28 (51)	33 (55)
Prognostic factors*						
Platinum-free interval, months						
< 3	14 (22)	18 (29)	16 (25)	17 (30)	16 (29)	16 (27)
≥ 3	49 (77)	44 (71)	47 (75)	39 (68)	38 (69)	44 (73)
ECOG performance status						
0	38 (59)	34 (55)	34 (54)	35 (61)	27 (49)	38 (63)
1 or 2	26 (41)	28 (45)	28 (44)	22 (39)	26 (47)	20 (33)
Baseline CA-125 ≥ 100 U/mL	46 (72)	45 (73)	46 (73)	46 (81)	42 (76)	45 (75)
Ascites at baseline	20 (31)	24 (39)	19 (30)	20 (35)	15 (27)	15 (25)
Measurable disease, SLD, cm						
< 1 or no lesion	13 (20)	11 (18)	13 (21)	11 (19)	12 (22)	15 (25)
1 to < 5	22 (34)	23 (37)	25 (40)	25 (44)	13 (24)	17 (28)
≥ 5	29 (45)	28 (45)	25 (40)	21 (37)	30 (55)	28 (47)

NOTE. All data are given as No. (%) unless otherwise specified.
Abbreviations: CA-125, cancer antigen–125; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; PLD, pegylated liposomal doxorubicin; SLD, sum of largest diameter.
*Identified as prognostic factors for overall survival; selected chemotherapy, as recorded in the case report form, was also identified as a prognostic factor.

v 14.1 months with chemotherapy alone) and 1.09 (95% CI, 0.72 to 1.67) for topotecan (median, 13.8 *v* 13.3 months). However, a more pronounced treatment effect on OS was seen in the paclitaxel cohort (unadjusted HR, 0.65; 95% CI, 0.42 to 1.02; median 22.4 *v* 13.2 months; Fig 1B). The extent of cross-over to bevacizumab from chemotherapy alone was similar in the three chemotherapy cohorts (paclitaxel, 38%; PLD, 39%; topotecan, 41%).

These findings, albeit generated in exploratory analyses of small subgroups, generate two questions. First, are there differences in the activity of the three chemotherapy regimens in PROC? And, second, is there an optimal chemotherapy partner for bevacizumab in PROC?

In the chemotherapy-only arm, numbers of PFS events, median PFS, and ORR seemed to differ between cohorts. Topotecan, typically given weekly, seemed less active than weekly paclitaxel, with intermediate results for PLD. This observation is aligned with data suggesting suboptimal efficacy of weekly topotecan,[3] whereas weekly paclitaxel induces high ORRs but disappointing PFS.[4-6] However, median OS with chemotherapy alone was similar between cohorts and consistent with historical data.

A major limitation of such comparisons is the lack of randomization to chemotherapy cohorts. One may expect imbalances in measured and unmeasured potentially prognostic factors among cohorts given that clinical, disease, and patient characteristics presumably influenced chemotherapy selection. In general, however, baseline characteristics were balanced, except for the proportion of patients who had received two previous chemotherapy regimens (Table 1). To further explore prognostic factors for OS, we fitted a multivariable Cox model starting with all covariates significant at 15% in a univariable model. Backwards selection at the 5% level provided the final model. Chemotherapy partner, performance status, ascites, disease measurability, baseline cancer antigen–125 value, and platinum-free interval were significant prognostic factors for OS. These factors were evenly distributed among chemotherapy cohorts and between treatment arms; this result suggested that the striking results with weekly paclitaxel were unlikely to be explained by patient population imbalances. Furthermore, OS in the intent-to-treat population after we adjusted for these prognostic factors was consistent with results of the unadjusted primary analysis.

In each chemotherapy cohort, the bevacizumab-chemotherapy combination significantly improved PFS, the primary end point, compared with chemotherapy alone, and it should be considered a new standard option for PROC. The US Food and Drug Administration and the European Commission approved bevacizumab combined with chemotherapy for PROC on the basis of results from AURELIA. However, interpretation of OS is less straightforward, complicated by study-design features, such as investigator-selected chemotherapy and optional cross-over to bevacizumab; other postprogression therapy; and the less-consistent treatment effects between cohorts. We observed no difference

in OS between treatment arms in the PLD and topotecan cohorts, but Kaplan-Meier curves for OS were clearly separated in the paclitaxel cohort. Experience with metastatic breast cancer suggests that bevacizumab combined with weekly paclitaxel may be more active than other backbones for chemotherapy.[7] Combining these two agents may enhance their antiangiogenic effects and potentially account for observations in AURELIA. In the front-line setting, this hypothesis was not supported in exploratory analyses of the GOG-262 trial.[8] However, the role of front-line weekly paclitaxel remains controversial.[9,10]

The main limitation of these exploratory analyses is that assessing individual chemotherapy partners for bevacizumab was not an objective of AURELIA. However, exploring consistency of effect in clinical trials is important, not necessarily for guiding treatment practice, but at least for hypothesis generation, particularly if a plausible biologic explanation for differences exists. Although consistency, on the basis of treatment effect estimates and 95% CIs, was seen between cohorts, the effect on PFS, ORR, and OS of combining bevacizumab with weekly paclitaxel was remarkable. These hypothesis-generating observations should be considered when investigators design new trials in PROC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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