Gynecologic Oncology 152 (2019) 61–67

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

# Real-world effectiveness of bevacizumab based on AURELIA in platinum-resistant recurrent ovarian cancer (REBECA): A Korean Gynecologic Oncology Group study (KGOG 3041)☆,☆☆

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## HIGHLIGHTS

- We conducted a multicenter, observational study in a real-world clinical setting.
- The effectiveness of bevacizumab was consistent with the results from AURELIA study.
- The effectiveness and toxicity profiles varied among the chemotherapy.

## ARTICLE INFO

*Article history:*
Received 10 August 2018
Received in revised form 18 October 2018
Accepted 23 October 2018
Available online 6 November 2018

*Keywords:*
Ovarian cancer
Platinum-resistant
Bevacizumab
Chemotherapy
Real world

## ABSTRACT

*Purpose.* To evaluate the effectiveness of bevacizumab with single-agent chemotherapy for platinum-resistant ovarian cancer in a real-world setting.

*Patients and methods.* We enrolled recurrent platinum-resistant ovarian cancer patients from 27 institutions. All had received bevacizumab with single-agent chemotherapy (weekly paclitaxel, pegylated liposomal doxorubicin (PLD), topotecan) between 2015 and 2017 for second- or third-line chemotherapy in routine clinical practice. The primary endpoint was progression-free survival (PFS) and safety. Secondary endpoints included the objective response rate (ORR), PFS2, overall survival, duration of chemotherapy, and reasons for discontinuing chemotherapy.

*Results.* Of 391 patients, 259 (66.2%) received bevacizumab with PLD, 94 (24.0%) with topotecan, and 38 (9.7%) with weekly paclitaxel. The median PFS was 6.1 months with all forms of bevacizumab-containing therapy. Although the cohort with weekly paclitaxel had a better PFS than the PLD cohort (P = 0.028), this finding was not found in patients with a previous platinum-free interval of less than three months. The median duration of therapy was five cycles (range, one to 20 cycles), and 29 patients (7.4%) discontinued treatment because of adverse events from bevacizumab-containing regimens. The PLD cohort had fewer grade ≥ 3 adverse events

☆ Presented April 27, 2018, in the plenary session of the 33rd annual meeting of the Korean Society of Gynecologic Oncology, Cheju, Republic of Korea.
☆☆ This work was supported by funding from Roche and Janssen (no grant number apply).
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https://doi.org/10.1016/j.ygyno.2018.10.031

than the other regimens (PLD, 35.8%; weekly paclitaxel, 52.6%; topotecan, 51.1%; P = 0.012), especially events of hematologic toxicities.

*Conclusion.* In Korean ovarian cancer patients, the safety and effectiveness of chemotherapy with bevacizumab in a real-world setting was consistent with the results from a randomized controlled study. The effectiveness and toxicity profiles varied among the chemotherapy regimens, and this finding should be considered in practice.

Clinical trials registration: NCT03367182.



## 1. Introduction

Bevacizumab, a humanized recombinant monoclonal antibody that inhibits vascular endothelial growth factor, has shown efficacy in the treatment of ovarian cancer. Five Phase III randomized clinical trials with a combination therapy of bevacizumab and chemotherapy have been conducted and resulted in the wide use of bevacizumab throughout multiple lines of therapy [1–5]. Results from the open-label, randomized Phase III AURELIA (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) trial demonstrated that combining bevacizumab with single-agent chemotherapy for treatment of platinum-resistant recurrent ovarian cancer (PR-ROC) significantly improved progression-free survival (PFS), the primary endpoint. A significant improvement occurred in the objective response rate (ORR) and in the patient-reported outcome end point of abdominal/GI symptoms in the intent-to-treat population of 361 patients [4]. The PFS HR (bevacizumab + chemotherapy vs. chemotherapy) estimates in the three cohorts were 0.46 (95% confidence interval [CI], 0.30–0.71) in the paclitaxel cohort (median PFS, 10.4 vs. 3.9 months), 0.57 (95% CI, 0.39–0.83) for PLD (median 5.4 vs. 3.5 months), and 0.32 (95% CI, 0.21–0.49) for topotecan (median 5.8 vs 2.1 months, respectively) [6]. Nevertheless, because none of the three approaches to treatment was randomized, the best chemotherapy partner for bevacizumab in PR-ROC remains unclear.

The Korean Food and Drug Administration (KFDA) has permitted the use of bevacizumab in a recurrent platinum-resistant setting since August 2015. Scant real-world data exist on clinical outcomes in which bevacizumab was used in large, unselected, general clinical practice populations, including those with elderly patients and other patients with less favorable prognostic factors than patients selected for clinical trials. At this time, real-world data on its effectiveness are needed to inform PR-ROC treatment decisions.

We conducted a multicenter, observational study in a real-world clinical setting to evaluate the effectiveness of treatment based on AURELIA. The aims of this study were to identify in a large retrospective analysis the effectiveness of treatment based on AURELIA and to establish the safety profile of bevacizumab, and define optimal chemotherapy partners.

## 2. Methods

### 2.1. Patients and study design

This was an observational study of Korean women with platinum-resistant recurrent ovarian cancer who between August 2015 and August 2017 received single-agent chemotherapy with bevacizumab in 27 institutions in Korea. In general, the eligibility criteria were designed to recruit a patient population similar to the one enrolled in AURELIA. All patients older than 18 with platinum-resistant recurrent ovarian cancer were eligible if during the study period they had received one of the following regimens in second- or third-line chemotherapy: weekly paclitaxel + bevacizumab, topotecan + bevacizumab, or PLD + bevacizumab. All patients were monitored until January 2018 for survival and discontinuation of bevacizumab.

This study was approved by the institutional review boards of the participating centers in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. It also is registered with ClinicalTrials.gov, number NCT03367182.

### 2.2. Treatment

Investigators chose their preferred chemotherapy for each patient from the following options, with appropriate premedication according to an institution's 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. Chemotherapy and bevacizumab were discontinued only in the face of disease progression, the occurrence of unacceptable toxicity, or at patients' request. Modifications of chemotherapy dosage were done at the clinicians' discretion.

### 2.3. Study assessments

Disease status was assessed at the outset to establish a baseline and then reassessed, using imaging, after every 3 cycles. Tumor markers were checked at every cycle. Additional imaging was used at the clinicians' discretion in such instances as when tumor markers were elevated.

### 2.4. Endpoints

All charts were reviewed retrospectively to collect clinical and laboratory data. In the multicenter observation retrospective study, the primary endpoint was investigator-assessed PFS by RECIST, defined as the interval between the day chemotherapy started and the first radiologically documented progression of the disease or death. The secondary endpoint included the ORR, defined as the proportion of patients who achieved a complete response (CR), plus those who achieved a partial response (PR), according to RECIST (version 1.1); PFS2 (calculated as the time from the day chemotherapy started and the occurrence of objective disease progression on next-line therapy or death from any cause); overall survival (OS; calculated as the time from the day chemotherapy started until death from any cause); safety, tolerability, duration of chemotherapy, and reasons for discontinuing chemotherapy. The associated reason was determined by the referring physician and classified as “disease progression,” “adverse event,” or “other reason.” For safety, adverse events (AEs) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0, Korean version). Safety analyses included all AEs occurring between the first dose administered in the study treatment and 30 days after the last dose.

### 2.5. Statistical analysis

The number of patients was calculated to detect any differences between the three arms containing bevacizumab. On a test at the 5% level (two sided) of significance ($\alpha$) and with 80% power, approximately 150 patients would be required to detect a similar difference in median PFS as was seen in the AURELIA study. Because our study was a retrospective

cohorts study to identify safety and effectiveness, we planned at the outset to collect at least 300 patients.

Categorical data were described by frequencies and percentages, and numerical data were described by means and standard deviations or medians and extreme values, if necessary. The Kaplan-Meier method was used to estimate PFS and OS. Hazard ratios (HRs) and 95% confidence intervals (Cis) for OS and PFS were estimated by using the Cox proportional hazard model. A logistic regression model was used to estimate ORRs. Because this was an observational study with a possible risk of bias associated with the selection of chemotherapy regimens, logistic regression was used to adjust the odds ratios for ORR for demographic variables such as age and treatment line.

## 3. Results

Between August 2015 and August 2017, 391 patients were treated. The data cutoff for this final analysis was January 2018; the median duration of follow-up was 13.6 months (range, 1–45 months). Investigator selection of chemotherapy was distributed as follows: Of the 391 patients, 259 (66.2%) received bevacizumab with PLD, and 94 (24.0%) with topotecan, and 38 (9.7%) with weekly paclitaxel. Patient disposition is shown in Fig. 1. Baseline characteristics are summarized in Table 1.

Bevacizumab was discontinued because of disease progression in 254 patients (65.0%), physicians' recommendations in 36 (9.2%), and patients' refusal in 17 (4.4%). Treatment was discontinued because of unacceptable toxicity in 29 (7.4%) (neutropenia and associated complications in 4 patients, hypertension in 6, proteinuria in 7, thromboembolic events in 2, gastrointestinal perforations in 2, bleeding in 2, a wound-healing complication in 1, a fistula/abscess in 1, and congestive heart failure in 4).

### 3.1. Efficacy

Response was evaluable by RECIST in 374 patients. The ORR was 32.9% with bevacizumab-containing therapy. The ORR was 31.3% in patients with responses evaluable by RECIST in second-line therapy (n = 205) and 34.9% in patients with responses evaluable by RECIST in third-line therapy (n = 169). The ORR was 48.6% versus 30.6%, respectively, for the weekly paclitaxel and PLD cohorts (P = 0.008). There was no statistically significant difference in ORR between the weekly paclitaxel and topotecan cohorts (P = 0.170) and the PLD and topotecan cohorts (P = 0.260) (Supplementary Fig. 1).

The bevacizumab-containing regimen showed a median PFS of 6.1 months (5.4 months for the PLD cohort; 8.3 months for the weekly paclitaxel cohort; and 7.0 months for the topotecan cohort). When comparing the 3 arms, the weekly paclitaxel cohort had a better PFS than the PLD arm (P = 0.028) and no statistically significant difference was found between the weekly paclitaxel and topotecan cohorts (P = 0.382) or the PLD and topotecan cohort (P = 0.070) (Fig. 2). This difference between the weekly paclitaxel and PLD cohorts was not found in patients with previous platinum-free intervals of <3 months (P = 0.319; data not shown). For OS, the topotecan cohort had significant better OS than the PLD cohort (P = 0.018) but no statistically significant difference in OS occurred between the weekly paclitaxel and PLD cohort (P = 0.779) or the weekly paclitaxel and topotecan cohort (P = 0.127). Median OS was 22 months (21 months for the PLD cohort; 21 months for the weekly paclitaxel cohort; and 25 months for the topotecan cohort).

For second-line therapy (n = 215, 55.0%), we found no significant difference of PFS in the three arms (PLD vs. weekly paclitaxel, P = 0.395; weekly paclitaxel vs. topotecan, P = 0.993; PLD vs. topotecan, P = 0.157). However, the PFS2 of the topotecan cohort was superior to the other regimen (weekly paclitaxel and PLD cohort; P < 0.001). The topotecan cohort also had superior OS to the PLD- bevacizumab arm (P = 0.005) and the weekly paclitaxel cohort (P = 0.014) (Supplementary Fig. 2). For third-line therapy (n = 176, 45%), we found no significant difference in either PFS or OS in the three arms (Supplementary Fig. 3).

As for recurrence, multivariate analysis showed that the weekly paclitaxel cohort had significant better PFS than the PLD cohort (HR 0.61; 95% CI, 0.40–0.95) but the topotecan cohort did not differ statistically from the PLD cohort (HR 0.78; 95% CI 0.59–1.04). Overall survival was significantly better statistically in the topotecan cohort than in the PLD cohort (HR 0.53; 95% CI, 0.32–0.89), whereas there was no statistically

**Table 1**
Baseline patient characteristics.

| | No. of patients (%) | | | |
|---|---|---|---|---|
| | All (n = 391) | w-P + bev (n = 38) | PLD + bev (n = 259) | Topo + bev (n = 94) |
| Age, years | | | | |
| Median (range) | 55 (23–82) | 55 (32–73) | 56 (23–82) | 53 (23–78) |
| Origin of cancer | | | | |
| Ovary | 344 (88.0) | 30 (79.0) | 231 (89.2) | 83 (88.3) |
| Tube | 22 (5.6) | 4 (10.5) | 15 (5.8) | 3 (3.2) |
| Peritoneum | 21 (5.4) | 4 (10.5) | 10 (3.9) | 7 (7.5) |
| Histology at diagnosis | | | | |
| HGSC | 277 (70.8) | 29 (76.3) | 182 (70.3) | 66 (70.2) |
| LGSC | 17 (4.4) | 3 (8.9) | 10 (3.9) | 4 (4.3) |
| Mucinous | 15 (3.8) | 1 (2.6) | 11 (4.3) | 3 (3.2) |
| Endometrioid | 12 (3.1) | 0 (0) | 8 (3.1) | 4 (4.3) |
| Clear cell | 40 (10.2) | 3 (7.9) | 27 (10.4) | 10 (10.6) |
| Grade | | | | |
| 1 | 30 (7.7) | 3 (7.9) | 23 (8.9) | 4 (4.3) |
| 2 | 67 (17.1) | 12 (31.6) | 45 (17.4) | 10 (10.6) |
| 3 | 265 (67.8) | 20 (52.6) | 170 (65.6) | 75 (79.8) |
| NA | 29 (7.4) | 3 (7.9) | 21 (8.1) | 5 (5.3) |
| BRCA status | | | | |
| No mutation | 156 (39.9) | 19 (50) | 106 (40.9) | 31 (33.0) |
| BRCA 1/2 mutation | 29 (7.4) | 3 (7.9) | 22 (8.5) | 4 (4.3) |
| BRCA VUS | 18 (4.6) | 1 (2.6) | 14 (5.4) | 3 (3.2) |
| Not checked | 188 (48.1) | 15 (39.5) | 117 (45.2) | 56 (59.6) |
| Bev regimen | | | | |
| 2nd line | 215 (55.0) | 12 (31.6) | 168 (64.9) | 35 (37.2) |
| 3rd line | 176 (45.0) | 26 (68.4) | 91 (35.1) | 59 (62.8) |
| Platinum-free interval* | | | | |
| <3 months | 166 (42.5) | 13 (34.2) | 196 (40.9) | 47 (50) |
| ≥3 months | 225 (57.5) | 25 (65.8) | 153 (59.1) | 47 (50) |
| Measurable disease | | | | |
| Yes | 194 (49.6) | 20 (52.6) | 133 (51.4) | 41 (43.6) |
| Ascites | | | | |
| Yes | 129 (33.0) | 5 (13.2) | 88 (34.0) | 36 (38.3) |

w-P, weekly paclitaxel; Topo, topotecan; bev, bevacizumab; VUS, variant unknown significance.

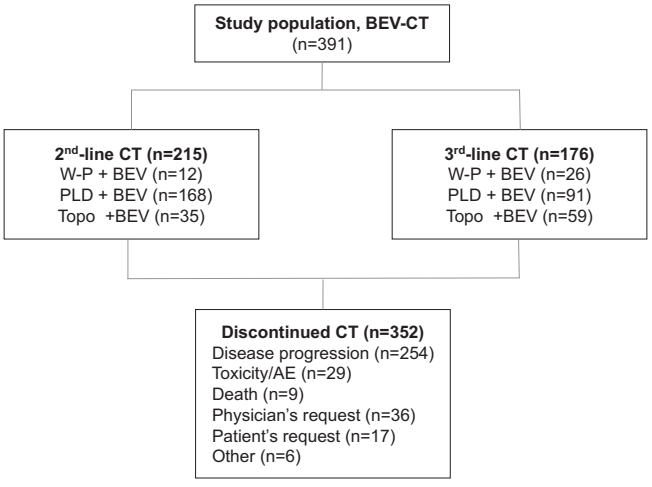


**Fig. 1.** Patient disposition. W-P, weekly paclitaxel; Topo, topotecan; AE, adverse event; BEV, bevacizumab; CT, chemotherapy.

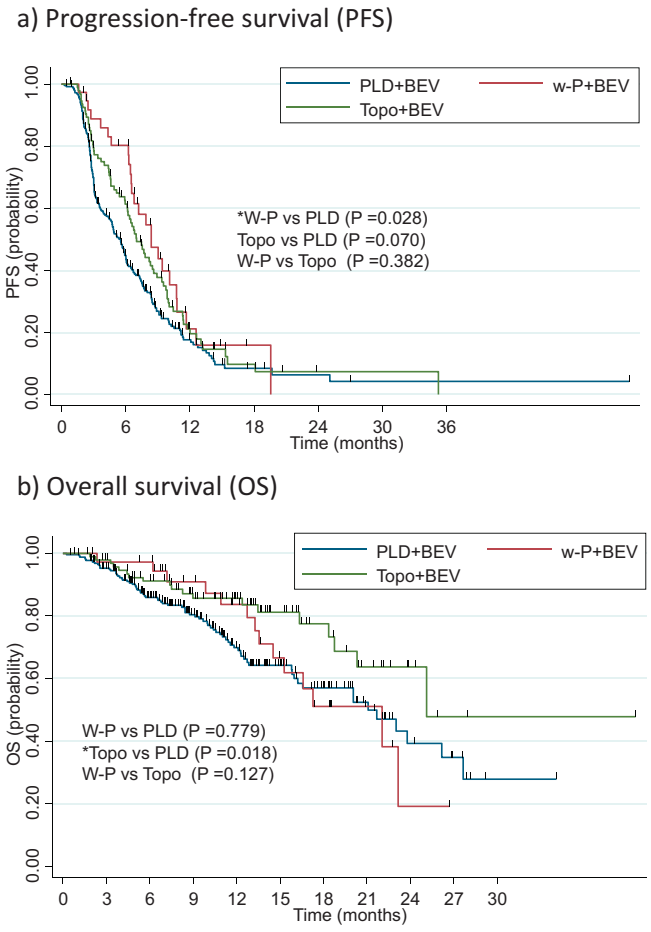


**Fig. 2.** Survival according to chemotherapy partner.

significant difference between the topotecan and weekly Paclitaxel cohorts (HR 1.10; 95% CI, 0.60–1.99) (Table 2).

### 3.2. Treatment exposure

The median duration of therapy was 5 cycles (range, 1 to 20 cycles) (Fig. 3). Chemotherapy exposure was lower in the PLD group (median 4 cycles) than in other groups (weekly Paclitaxel group median; 6 cycles, topotecan group; median 6 cycles), reflecting short PFS in PLD-treated patients.

### 3.3. Safety

The safety population included 391 patients, 386 of whom were included in the safety analysis. Adverse events of special interest (reported in previous bevacizumab clinical trials) and grade ≥ 3 adverse events are summarized in Table 3. Grade ≥ 2 hypertension was found in 9.6% of the safety population. There were fewer cases of grade ≥ 2 hypertension in the topotecan cohort than in other regimens (P = 0.006). Similarly, grade ≥ 2 proteinuria was found in 7.8% of the safety population, but there were fewer cases of grade ≥ 2 proteinuria in the topotecan cohort than in the other regimens (P = 0.018). Grade ≥ 3 gastrointestinal perforations were observed in 5 patients of the study population.

Grade ≥ 3 adverse events (AEs) occurred in 41.2% of the safety analysis population: Grade 3 in 103 patients (26.7%), grade 4 in 51 patients (13.2%), and grade 5 in 5 patients (1.3%). Two of the fatal AEs occurred during concurrent chemotherapy (1 thromboembolic event and 1 gastrointestinal perforation). The most common grade 3 or higher-grade AEs were neutropenia (reported as a clinical AE [28.0%]), thrombocytopenia (9.8%), and hypertension (5.2%). Grade ≥ 3 AEs were less frequently observed in the PLD cohort than in other regimens (PLD, 35.8%; weekly paclitaxel, 52.6%; topotecan, 51.1%; P = 0.012) (Supplementary Fig. 4). Specifically, hematologic toxicity occurred less in the PLD cohort. Grade ≥ 3 neutropenia was found in 18.9% of the PLD cohort (42.9% in the weekly paclitaxel cohort and 45.7% in the topotecan cohort). In addition, grade ≥ 3thrombocytopenia was found in 6.9% of the PLD cohort (6.7% in weekly paclitaxel cohort and 20.4% in topotecan cohort) and grade ≥ 3 anemia was found in 4.4% of the PLD cohort (5.3% in the weekly paclitaxel cohort and 14.9% in the topotecan cohort). Hand-foot syndrome occurred in 13.1% of the PLD cohort (Grade 1 in 12 (4.9%) patients; Grade 2 in 17 (6.9%) patients; and Grade 3 in 3 (1.2%) patients).

During the study period, five patients (1.3%) died of causes not attributed primarily to progressive disease. Three were from infection with neutropenia, one from sepsis from a bowel perforation, and one from a stroke. Two of the fatal AEs occurred during treatment (1 thromboembolic event and 1 gastrointestinal perforation).

**Table 2**
Multivariate analysis.

| | Recurrence | | Death | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| PLD + bev | Reference | | Reference | |
| w-P + bev | 0.61 | 0.40–0.95 | 1.1 | 0.66–1.99 |
| Topo + bev | 0.78 | 0.59–1.04 | 0.53 | 0.32–0.89 |

Adjusted for stage, grade, histology, age at diagnosis, platinum-free interval, measurable disease, and ascites.
w-P, weekly paclitaxel; Topo, topotecan; bev, bevacizumab; HR, hazard ratio.

## 4. Discussion

In the context of general oncology practice, this report represents the largest study population of patients with platinum-resistant recurrent ovarian cancer receiving bevacizumab-containing therapy. Its results show that a bevacizumab-containing regimen is well-tolerated, with a low incidence of serious AEs or specific AEs. The effectiveness and safety profile are generally consistent with results from the AURELIA randomized Phase III trials.

Bevacizumab is now incorporated into all lines of ovarian cancer management. On the basis of the results from AURELIA, the FDA of the United States and the European Commission have approved treatment with bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer. Treatment with bevacizumab for platinum-resistant recurrent ovarian cancer has been approved in Korea since 2015. Despite debates about its cost-effectiveness because of its high cost [7–9], the insurer covers the costs of the drug in Korea; the National Health Insurance (NHI) accepts 95% of the total cost, and the patient pays 5%. Therefore, because many clinicians have adopted bevacizumab in this setting, we could quickly collect a large number of individuals being treated with bevacizumab.

In this retrospective cohort study evaluating the effectiveness of a bevacizumab-containing regimen, the median duration of bevacizumab exposure and the median PFS were slightly shorter than in AURELIA. (In our study, the median duration of bevacizumab was 5 cycles and the median PFS was 6.1 months compared in the AURELIA study with a median duration of bevacizumab exposure of 6 cycles and a median PFS of 6.7 months.) This small difference may be partly explained by the worse prognosis of patients in our REBECA study as the prevalence of patients with platinum-free intervals of less than three months was higher in our study than in AURELIA (42.5% vs. 25.2% in AURELIA). The study population in REBECA was of general oncology practice than populations enrolled in randomized trials such as AURELIA. Considering that disease progression was the most common reason for discontinuing

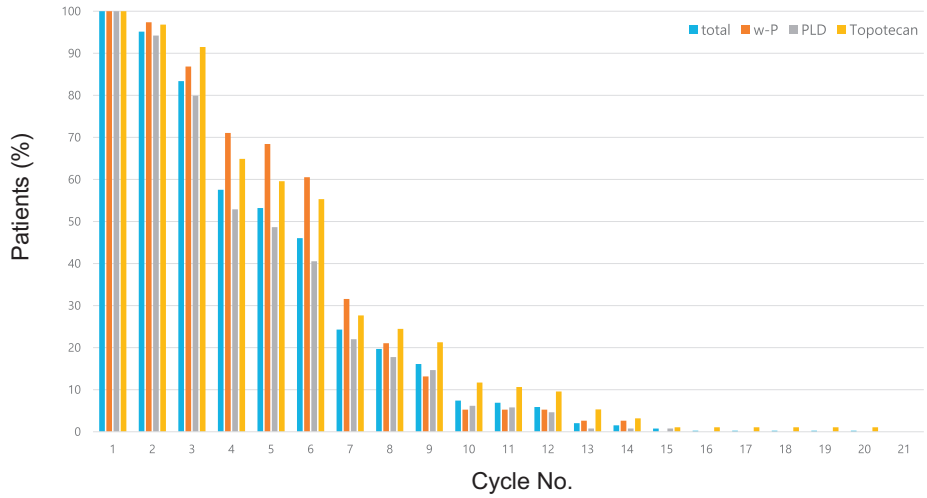


**Fig. 3.** Summary of treatment exposure.

bevacizumab, this discrepancy between a real-world setting and a randomized study is understandable.

Exploratory analysis from AURELIA showed that survival outcomes such as ORR, PFS, and OS were remarkable in the paclitaxel cohort [6]. AURELIA analysis could not determine an optimal chemotherapy partner for bevacizumab because of the previously mentioned lack of randomization. Because additional RCTs to address this issue are unlikely anytime soon, we have tried to use this retrospective analysis to make this partnership determination.

We have shown that the ORR by RECIST was higher in the weekly paclitaxel cohort than in any other cohort, a result consistent with that reported in AURELIA. Similarly, the weekly paclitaxel cohort showed better PFS than the PLD cohort. However, we found better PFS2 and OS in the topotecan cohort. As the topotecan benefit in the second-line regimen was not anticipated, we evaluated the third-line therapy of patients who received topotecan-bevacizumab as a second-line regimen and found that the ORR was 25.9% from third-line therapy (Supplementary Table 1). Our cohort did not include a second round of treatment with bevacizumab because KFDA did not allow its reuse. Furthermore, most patients within the topotecan cohort (94.7%, 89/94) were treated with a regimen of 1.25 mg/m$^2$ on days 1 to 5 every 3 weeks rather than a regimen of 4 mg/m$^2$ weekly. In the AURELIA study, only 22% of 120 patients treated in the topotecan cohort received a regimen of 1.25 mg/m$^2$ on days 1 to 5 every 3 weeks rather than a regimen of 4 mg/m$^2$ weekly. Because the weekly regimen of topotecan was less active than the daily regimen, the discrepancy between AURELIA and our study in the topotecan cohort may be explained by the different topotecan regimens used in the two studies [10].

The safety profile was generally consistent with the experience from the randomized Phase III trial, and the grade ≥ 3 adverse events were acceptable in light of the real-world experience. Furthermore, the dropout rate because of toxicity was lower in our study than in AURELIA (7.4% in REBECA vs. 27.4% in AURELIA). This finding was also shown in the front-line real-world practice setting, and adverse events rarely led to treatment discontinuation [11]. There are differences in the safety profiles, depending on the chemotherapy partners. In our study, the PLD cohort had less hematologic toxicity than other regimens. Although the weekly paclitaxel and daily topotecan regimens showed relatively better activity than the PLD cohort, the inconvenience of the chemotherapy schedule and the toxicity from the regimens should be discussed with patients before choosing a chemotherapy regimen.

This study has some limitations, such as those inherent in the design of an observational study, and selection biases may have affected the results. Physicians chose the chemotherapy regimens, and doses were modified at physicians' discretion. Because of these limitations, the apparent differences in safety and effectiveness according to chemotherapy partners should be interpreted cautiously.

In summary, results from this large observational study indicate that bevacizumab-containing chemotherapy is both tolerable and feasible for platinum-resistant ovarian cancer in real- world clinical practice. The effectiveness and toxicity profiles vary according to the chemotherapy partner, and this finding should be considered.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.10.031.

**Table 3**
Summary of grade ≥ 3 (and selected grade ≥ 2) AEs of special interest.

| | Grade 2 | Grade ≥ 3 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Any AE of special interest | | 159 (41.2%) | 103 (26.7%) | 51 (13.2%) | 5 (1.3%) |
| Neutropenia and associated complications | | 108 (28.0%) | 58 (15.0%) | 47 (12.2%) | 3 (0.8%) |
| Hypertension (grade ≥ 2) | 17 (4.4%) | 20 (5.2%) | 20 (5.2%) | 0 (0%) | 0 (0%) |
| Thrombocytopenia | | 38 (9.8%) | 23 (6.0%) | 15 (3.9%) | 0 (0%) |
| Proteinuria (grade ≥ 2) | 20 (5.2%) | 10 (2.6%) | 10 (2.6%) | 0 (0%) | 0 (0%) |
| Thromboembolic events | | 5 (1.3%) | 4 (1.0%) | 0 (0%) | 1 (0.3%) |
| Gastrointestinal perforation (grade ≥ 2) | 6 (1.6%) | 5 (1.3%) | 3 (0.8%) | 1 (0.3%) | 1 (0.3%) |
| Bleeding | | 3 (0.8%) | 2 (0.5%) | 1 (0.3%) | 0 (0%) |
| Wound healing complication | | 3 (0.8%) | 2 (0.5%) | 1 (0.3%) | 0 (0%) |
| Fistula/abscess (grade ≥ 2) | 0 (0%) | 2 (0.5%) | 2 (0.5%) | 0 (0%) | 0 (0%) |
| Congestive heart failure | | 2 (0.5%) | 1 (0.3%) | 1 (0.3%) | 0 (0%) |
| Posterior reversible encephalopathy syndrome | | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Other | | 4 (1.0%) | 4 (1.0%) | 0 (0%) | 0 (0%) |

AE, adverse events.

## Role of funding source

The first author designed the trial in collaboration with the study funder. The sponsors were involved in the design of the study, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to the study data and are responsible for the accuracy of the data and interpretation of the results. The corresponding author had final responsibility for the decision to submit for publication.

## Research funding

Jung-Yun Lee, Roche, Janssen.

## Disclosure

Jung-Yun Lee has received research funding from AstraZeneca, Roche, and Janssen Korea Ltd.

Eric Pujade-Lauraine reported personal fees and non-financial support from Hoffman-LaRoche, AstraZeneca, Tesaro, and Clovis.

All remaining authors declare no conflict of interest.

## Author contributions

Jung-Yun Lee: Conception and design, provision of study materials of patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript.

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## Acknowledgments

We thank all patients and their families, the investigators and study teams at the participating sites, the Roche medical team, and the Janssen medical team.

We are indebted to the following investigators who participated in this study.

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