Received: 20 July 2021 | Revised: 4 October 2021 | Accepted: 20 October 2021

DOI: 10.1111/cas.15185

Cancer Science WILEY

ORIGINAL ARTICLE

Efficacy and safety of standard of care with/without bevacizumab for platinum-resistant ovarian/fallopian tube/peritoneal cancer previously treated with bevacizumab: The Japanese Gynecologic Oncology Group study JGOG3023

Tadahiro Shoji[1] | Takayuki Enomoto[2] | Masakazu Abe[3] | Aikou Okamoto[4] | Takayuki Nagasawa[1] | Tetsuro Oishi[5] | Satoru Nagase[6] | Masahiko Mori[7] | Yuki Inokuchi[8] | Shoji Kamiura[9] | Shinichi Komiyama[10] | Nobuhiro Takeshima[11] | Toru Sugiyama[12]

[1]Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Iwate, Japan

[2]Department of Obstetrics and Gynecology, Niigata University School of Medicine, Niigata, Japan

[3]Department of Gynecology, Shizuoka Cancer Center, Shizuoka, Japan

[4]Department of Obstetrics and Gynecology, The Jikei University School of Medicine, Tokyo, Japan

[5]Department of Obstetrics and Gynecology, Tottori University School of Medicine, Tottori, Japan

[6]Department of Obstetrics and Gynecology, Faculty of Medicine, Yamagata University, Yamagata, Japan

[7]Department of Gynecology, Aichi Cancer Center Hospital, Aichi, Japan

[8]Department of Biostatistics, Kitasato Academic Research Organization, Kitasato University, Tokyo, Japan

[9]Department of Gynecologic Oncology, Osaka International Cancer Institute, Osaka, Japan

[10]Department of Obstetrics and Gynecology, Faculty of Medicine, Toho University, Tokyo, Japan

[11]Department of Gynecology, Cancer Institute Hospital, Tokyo, Japan

[12]Department of Obstetrics and Gynecology, St. Mary's Hospital, Fukuoka, Japan

Correspondence
Tadahiro Shoji, Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, 2-1-1 Idaidori, Yahaba, Iwate 028-3695, Japan.
Email: tshoji@iwate-med.ac.jp

Present address
Masakazu Abe, Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, Shizuoka, Japan

Funding information
Chugai Pharmaceutical Co., Ltd

Abstract

We investigated the efficacy and safety of further bevacizumab therapy in patients with platinum-resistant ovarian cancer whose disease had progressed after bevacizumab plus chemotherapy. In this multicenter, open-label, phase II trial (JGOG3023), patients were randomized 1:1 to a single-agent chemotherapy alone (either pegylated liposomal doxorubicin [40 or 50 mg/m^2 administered intravenously], topotecan [1.25 mg/m^2 intravenously], paclitaxel [80 mg/m^2 intravenously], or gemcitabine [1000 mg/m^2 intravenously]) or single-agent chemotherapy + bevacizumab (15 mg/m^2 intravenously). The primary endpoint was investigator-assessed progression-free survival (PFS) according to RECIST version 1.1. Secondary endpoints were

Abbreviations: AEs, adverse events; CA, cancer antigen; CI, confidence interval; GCIG, Gynecological Cancer Intergroup; GEM, gemcitabine; HR, hazard ratio; ITT, intent-to-treat; JGOG, Japanese Gynecologic Oncology Group; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PPS, per protocol set; SAS, safety analysis set.

Trial registration: UMIN Clinical Trials Registry UMIN000017247

overall survival (OS), objective response rate (ORR), and response rate according to Gynecological Cancer Intergroup cancer antigen 125 criteria. In total, 103 patients were allocated to chemotherapy (n = 51) or chemotherapy + bevacizumab (n = 52). Median investigator-assessed PFS was 3.1 and 4.0 mo in each group, respectively (hazard ratio [HR] = 0.54, 95% confidence interval [CI]: 0.32-0.90, $P = .0082$). Median OS was 11.3 and 15.3 mo in each group, respectively (HR = 0.67, 95% CI: 0.38-1.17, $P = .1556$). Respective ORRs were 13.7% and 25.0% ($P = .0599$) and response rates were 16.7% and 21.4% ($P = .8273$). The incidence of grade ≥3 treatment-related AEs was 42.0% in the chemotherapy group and 54.9% in the chemotherapy + bevacizumab group; AEs were well tolerated, with only 2 and 12 events leading to discontinuation of therapy, respectively. Bevacizumab was effective beyond progressive disease and AEs were manageable. The observed improvement in PFS requires further verification.

KEYWORDS
bevacizumab, fallopian tube cancer, ovarian cancer, peritoneal cancer, platinum resistance

1 | INTRODUCTION

Globally, the incidence of ovarian cancer is increasing every year,[1] and because most cases are diagnosed at an advanced stage, these patients tend to have a poor prognosis. The standard of care for ovarian cancer includes surgery plus chemotherapy with platinum and taxane agents.[2] However, 25% of patients at first relapse experience platinum resistance, and almost all patients who experience recurrence or progressive disease subsequently develop platinum-resistant disease.[3] Platinum-resistant recurrent ovarian cancer has a poor prognosis and a short OS of less than 12 mo.[4] There are limited treatment options for these patients, and available treatments do not necessarily prolong survival. The most common treatments for platinum-resistant ovarian cancer are PLD, topotecan, paclitaxel, and gemcitabine (GEM).[5] However, overall response rates are no greater than 15% and the median PFS is only 3-4 mo.[4] Therefore, new treatments are needed for platinum-resistant ovarian cancer.

Bevacizumab is a recombinant humanized monoclonal antibody that limits angiogenesis by inhibiting vascular endothelial growth factor. Bevacizumab is currently the standard for both the primary treatment of ovarian cancer[6,7] and the treatment of subsequent relapse.[8-10] Previous trials have demonstrated the clinical usefulness of administering bevacizumab beyond progressive disease in locally recurrent or metastatic breast cancer and in advanced or recurrent colorectal cancer.[11-13] The efficacy of continuing bevacizumab beyond progressive disease (ie, re-treatment with bevacizumab after progression of disease when previously treated with bevacizumab) was demonstrated in patients with platinum-sensitive recurrent ovarian cancer in a randomized phase III study; the study results showed a PFS of 11.8 mo and 8.8 mo with and without bevacizumab, respectively, with no unexpected toxicity.[14] Currently, however, there are no clinical trials of bevacizumab beyond progressive disease in patients with platinum-resistant recurrent ovarian cancer.

The present study sought to investigate the efficacy and safety of chemotherapy with or without bevacizumab in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who were previously treated with bevacizumab for front-line or platinum-sensitive ovarian cancer.

2 | MATERIALS AND METHODS

2.1 | Study design

Details of the study design and rationale have been published previously.[15] In brief, this was an open-label, parallel-arm, randomized, phase II trial conducted at Japanese Gynecologic Oncology Group institutions (JGOG3023).

Patients with platinum-resistant recurrent ovarian cancer and recurrence after bevacizumab therapy in combination with chemotherapy were randomly assigned 1:1 by dynamic randomization (minimization method) to treatment with single-agent chemotherapy (control arm: chemotherapy group) or single-agent chemotherapy plus bevacizumab (experimental arm: chemotherapy + bevacizumab group). Platinum resistance was defined as progression within 6 mo after the completion of at least 3 cycles of platinum-based chemotherapy, including bevacizumab. This definition therefore also includes patients that were characterized with platinum-refractory disease, which was defined as progression within 28 d of completing platinum-based chemotherapy. Patients with a measurable lesion confirmed by diagnostic imaging or with a cancer antigen (CA)125 level more than 2 times higher than normal were considered eligible.

The attending physician selected 1 of the following single-agent chemotherapy drugs for patients in both groups: PLD, topotecan, paclitaxel, or GEM. Randomization was performed according to the following stratification factors: number of regimens received previously (1 or 2 vs 3), time to recurrence or disease progression from the last day of platinum-drug administration (during treatment vs <3 mo vs ≥3 mo), and anticancer agent (PLD vs topotecan vs paclitaxel vs GEM).

Details of dosing schedules, criteria for discontinuation/modification of the chemotherapy regimens, and prohibited/allowed concomitant drugs have been described in detail previously.[15] Briefly, the dosing schedule for each chemotherapy regimen was as follows and each cycle was repeated until disease progression: PLD was administered intravenously at 40 mg/m^2 or 50 mg/m^2, 1 mg/min on Day 1 with a cycle equal to 28 d; topotecan was administered intravenously at 1.25 mg/m^2 for more than 30 min on Days 1, 2, 3, 4, and 5 with a cycle equal to 21 d; paclitaxel was administered intravenously at 80 mg/m^2 for 60 min on Days 1, 8, and 15 with a cycle equal to 21 d; and GEM was administered intravenously at 1000 mg/m^2 for 30 min on Days 1 and 8 with a cycle equal to 21 d. Chemotherapy regimens were discontinued or modified based on the presence of AEs, and the dose could also be reduced at the discretion of the attending physician. The bevacizumab dose could only be reduced or adjusted based on the patient's body weight. The following drugs and therapies were prohibited: anticancer treatment, including chemotherapy drugs other than those defined in this trial, endocrine therapy, radiation therapy, hyperthermia therapy, and surgery; drugs not approved or those under clinical trials for new drug application; and drugs and therapy thought to affect the safety and efficacy of the drugs of this trial. Antiemetics, treatments for AEs (including bisphosphonate and anti-RANKL antibody for the treatment of bone metastases), and anticoagulants were permitted, but only for prophylactic use.

This study was approved by the institutional review board of each participating JGOG institution and was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, the Ethical Guideline for Medical and Health Research involving Human Subjects, the Declaration of Helsinki, and applicable local laws and regulations. All patients provided written informed consent.

2.2 | Patients

A full list of the inclusion and exclusion criteria have been described previously.[15] The critical inclusion criteria were as follows: age ≥20 y with histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma; treated with ≥3 cycles of bevacizumab + platinum chemotherapy; progression occurred <6 mo after completion of platinum treatment; ECOG PS of 0-2; and RECIST progression with measurable lesion, or patients with non-measurable disease who could be evaluated based on Gynecological Cancer Intergroup (GCIG) CA125 criteria.

Critical exclusion criteria were as follows: ovarian borderline malignant tumor; history of other clinically active malignancy within 5 y of enrollment; ≥4 previous anticancer regimens; history of bowel obstruction (including sub-occlusive disease, related to the underlying disease, and history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess); pelvic examination showing evidence of rectosigmoid involvement, computed tomography showing bowel involvement, or symptoms of bowel obstruction; surgery within 28 d prior to the study start or need for major surgery during study treatment; need of palliative radiotherapy <14 d prior to the study start; current or recent treatment with another investigational drug within 30 d of the first study treatment dosing; known hypersensitivity to any of the study drugs or excipients; pregnancy, lactation, or childbearing potential in women not using highly effective contraception; and judgment by the principal investigator of inappropriateness to participate in the trial.

2.3 | Efficacy

The primary endpoint was investigator-assessed PFS (at study completion or at the time point when at least 90 events of disease progression or death are observed) according to RECIST v1.1[16] or GCIG CA125 criteria.[17] Computed tomography scans were performed every 6 wk after the start of treatment. Secondary endpoints were as follows: OS censored on the day of the final dose of study treatment or death; ORR based on the response definition of RECIST v1.1 or GCIG CA125 criteria; response rate based on GCIG CA125 criteria; and the number of times paracentesis was performed.

2.4 | Safety

The incidence and severity of AEs and treatment-related AEs were evaluated according to the Common Toxicity Criteria for Adverse Events v4.0 JCOG Japanese version (CTCAE v4.0-JCOG).[18]

2.5 | Statistical analysis

Details of the statistical analysis have been described previously.[15] In summary, the sample size was set to compare PFS, the primary endpoint, and the median PFS of the control group was assumed to be 3 mo. The HR of the treatment group to the control group was expected to be 0.7; the median PFS of the treatment group corresponding to an HR equal to 0.7 was approximately 4.3 mo. The survival time of each group was assumed to follow an exponential distribution. With an allocation ratio to the chemotherapy and chemotherapy + bevacizumab groups set at 1:1, 90 events would be required to ensure a statistical power of ≥80% in the log-rank test with a 1-sided significance level of 20%. As it was anticipated that it

would be difficult to secure a sufficient sample size with a two-sided significance level of .05, we set the 1-sided significance level at .2 to improve detection power. We assumed that the objectives of this randomized phase 2 clinical trial justify this approach. Considering a registration period of 24 mo, which was initially planned, and a minimum PFS observation period of 6 mo, 97 patients would be required to observe 90 events. Therefore, the target number of patients was determined to be 106 (approximately 53 patients per group).

The analysis populations were the ITT set (defined as patients who were registered to this study and randomly allocated to either of the groups), the PPS (defined as patients among the ITT set who received the protocol therapy at least once and had no serious protocol deviation), and the SAS (defined as patients who were registered to this study and received the protocol therapy at least once).

Descriptive statistics were used for baseline demographic and clinical characteristics, with n (%) for categorical variables and mean ± SD for continuous variables. In each group, the median PFS and OS and their respective 95% CI (two-sided) were estimated by the Kaplan-Meier method. Statistical significance between the groups was evaluated by the stratified log-rank test with a significance level of 20% (one-sided) for PFS and 5% (two-sided) for OS. A stratified Cox proportional hazard model was used for estimating the adjusted HR and its 95% CI (two-sided). A multivariable Cox proportional hazard model was constructed using treatment allocation, each factor, and their interactions as explanatory variables to test whether the coefficient of the interaction term was zero. A two-sided significance level of 20% was used. ORR was evaluated in patients with evaluable response according to the RECIST v1.1 criteria. A Cochran-Mantel-Haenszel test was used to assess between-group statistical significance, with a significance level of 5% (two-sided). ORR and its 95% Clopper-Pearson CI (two-sided) were calculated for each group.

A multivariable logistic regression model was used to estimate the adjusted odds ratio between treatment groups. The median number of paracentesis procedures performed and the percentage of patients who underwent paracentesis were determined. Statistical significance between the groups was calculated by the van Elteren test (stratified Wilcoxon rank sum test), with a significance level of 5% (two-sided). The statistical software used for statistical analysis was SAS version 9.3 (SAS Institute Inc, Cary, NC, USA).

3 | RESULTS

3.1 | Patient disposition and characteristics

The study was conducted from June 2015 to November 2019. The enrollment period was initially planned for 2 y but was extended to 3.5 y to reach the sample size required; the follow-up period was 6 mo after completion of patient registration. The patient disposition is shown in Figure 1. In total, 103 patients were enrolled and allocated to the chemotherapy group (n = 51) and chemotherapy + bevacizumab group (n = 52); all of these patients were included in the ITT analysis set. Two patients in the chemotherapy + bevacizumab group were discontinued before starting protocol treatment. Two patients were misallocated to the chemotherapy group and received bevacizumab. These patients were included in the chemotherapy group for efficacy analyses and in the chemotherapy + bevacizumab group for safety analyses. One patient allocated to the chemotherapy + bevacizumab group received chemotherapy alone (without bevacizumab). This patient was included in the chemotherapy + bevacizumab group for efficacy analysis and the chemotherapy group for safety analysis. The efficacy analyses were done using the ITT set. For the safety analysis, 50 patients (chemotherapy group) and 51 patients (chemotherapy + bevacizumab group) were included in the SAS.

The baseline demographic and clinical characteristics of the study patients are summarized in Table 1. The mean ± SD age of patients was 60.7 ± 12.15 y in the chemotherapy group and 60.3 ± 9.71 y in the chemotherapy + bevacizumab group. Serous carcinoma was the most common histological category in both groups. Twelve patients in each group had a platinum-free interval of zero during the study treatment and use of bevacizumab as a front-line therapy was similar in both groups. Baseline characteristics were well balanced between groups.

3.2 | Efficacy

3.2.1 | Primary endpoint

The median investigator-assessed PFS (primary endpoint) was 3.1 mo (95% CI: 2.5-4.6) in the chemotherapy group and 4.0 mo (95% CI: 3.0-5.7) in the chemotherapy + bevacizumab group (HR = 0.54, 95% CI: 0.32-0.90, 1-sided $P = .0082$) (Figure 2A). In the multivariate Cox regression model of PFS, using the 20% significance level, interactions with treatment allocation were detected for the maximum tumor diameter (≥50 mm vs <50 mm) ($P = .0158$) and presence of ascites ($P = .1866$) (Figure 2B). The HR of the chemotherapy + bevacizumab group relative to the chemotherapy group was 0.18 (95% CI: 0.03-1.05) in the subgroup with a maximum tumor diameter of ≥50 mm (n = 10) and 0.85 (95% CI: 0.52-1.39) in the subgroup with a maximum tumor diameter of <50 mm (n = 66).

3.2.2 | Secondary endpoints

The median OS was 11.3 mo (95% CI: 8.8-12.6) in the chemotherapy group and 15.3 mo (95% CI: 10.0-17.4) in the chemotherapy + bevacizumab group (HR = 0.67, 95% CI: 0.38-1.17, $P = .1556$) (Figure 3A). In the multivariate Cox regression model of OS, using the 20% significance level, interactions with treatment allocation were detected for the number of previous regimens (1 or 2 vs ≥3) ($P = .1215$) and the maximum tumor diameter (≥50 mm vs <50 mm) ($P = .0689$) (Figure 3B).

Response was evaluated in 77 patients (39 in the chemotherapy group and 38 in the chemotherapy + bevacizumab group) by the definition of RECIST v1.1 and in 26 patients (12 in the chemotherapy

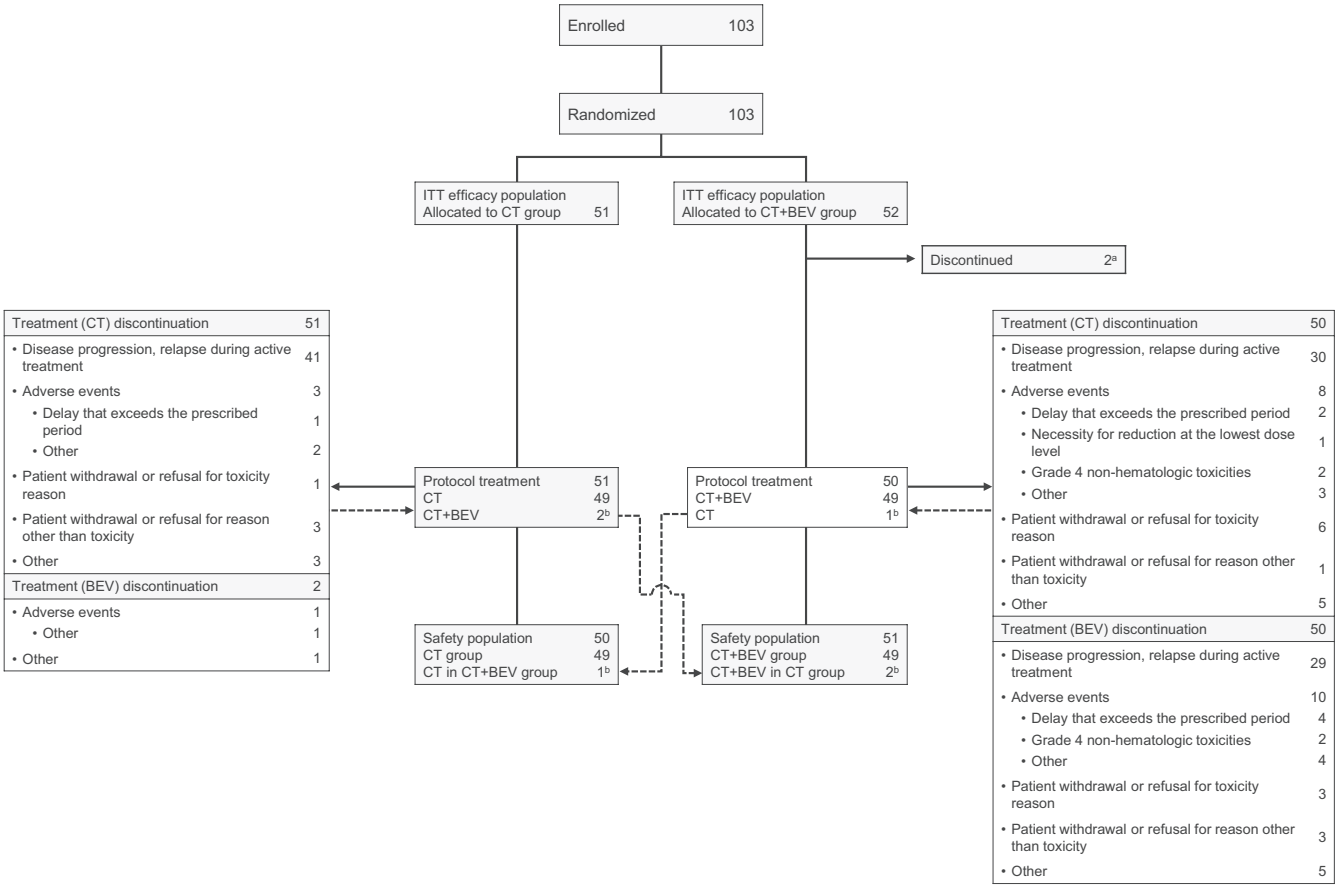


FIGURE 1 Patient disposition. Data are n (%). [a]The reasons for discontinuation were as follows. In 1 case, the dosing regimen assigned to the patient was not approved. In another case, the patient's protein to creatinine ratio (1.3) was found to be above that established as an eligibility criterion for this study (≤1.0). [b]Two patients were misallocated to the chemotherapy group and received bevacizumab; these patients were included in the chemotherapy group for efficacy analyses and in the chemotherapy + bevacizumab group for safety analyses. One patient allocated to the chemotherapy + bevacizumab group received chemotherapy alone (without bevacizumab) and was included in the chemotherapy + bevacizumab group for efficacy analysis and the chemotherapy group for safety analysis. BEV, bevacizumab; CT, chemotherapy; ITT, intention to treat

group and 14 in the chemotherapy + bevacizumab group) by the GCIG CA125 criteria. The ORR defined by the RECIST was 13.7% (95% CI: 5.7%-26.3%) in the chemotherapy group (complete response, n = 0; partial response, n = 7) and 25.0% (95% CI: 14.0%-38.9%) in the chemotherapy + bevacizumab group (complete response, n = 1; partial response, n = 12) (P = .0599). Furthermore, the response rate according to the GCIG CA125 criteria was 16.7% (95% CI: 2.1%-48.4%) in the chemotherapy group and 21.4% (95% CI: 4.7%-50.8%) in the chemotherapy + bevacizumab group (P = .8273).

3.3 | Safety

A summary of AEs and treatment-related AEs is shown in Table 2. The overall incidence of AEs was 100% in the chemotherapy group and 98.0% in the chemotherapy + bevacizumab group, and that of treatment-related AEs was 96.0% in the chemotherapy group and 96.1% in the chemotherapy + bevacizumab group. The AEs were generally manageable; only 2 patients in the chemotherapy group and 12 patients in the chemotherapy + bevacizumab group discontinued treatment due to AE.

There were more treatment-related grade ≥3 AEs in the chemotherapy + bevacizumab group compared with the chemotherapy group (54.9% vs 42.0%). One patient in the chemotherapy + bevacizumab group died due to an AE (infection or infestation – other). The patient had a fever of 39°C during Cycle 2 of PLD + bevacizumab therapy and received appropriate inpatient management. Further chemotherapy was cancelled. On Day 28 of the second administration of bevacizumab, the patient experienced a massive melena, which was considered an AE possibly attributable to bevacizumab. Later, the patient presented with neutrophil count decreased and grade 4 platelet count decreased. Although symptomatic treatment was provided, the patient died of bacteremia. Neutrophil count decreased and platelet count decreased were AEs possibly attributable to PLD; therefore, the attending physician reported that the death was attributable to both bevacizumab and PLD.

The incidence of grade 4 AEs was low and included stroke (n = 1) in the chemotherapy group, and duodenal perforation (n = 1) and

TABLE 1 Baseline demographic and clinical characteristics (intent-to-treat analysis set)

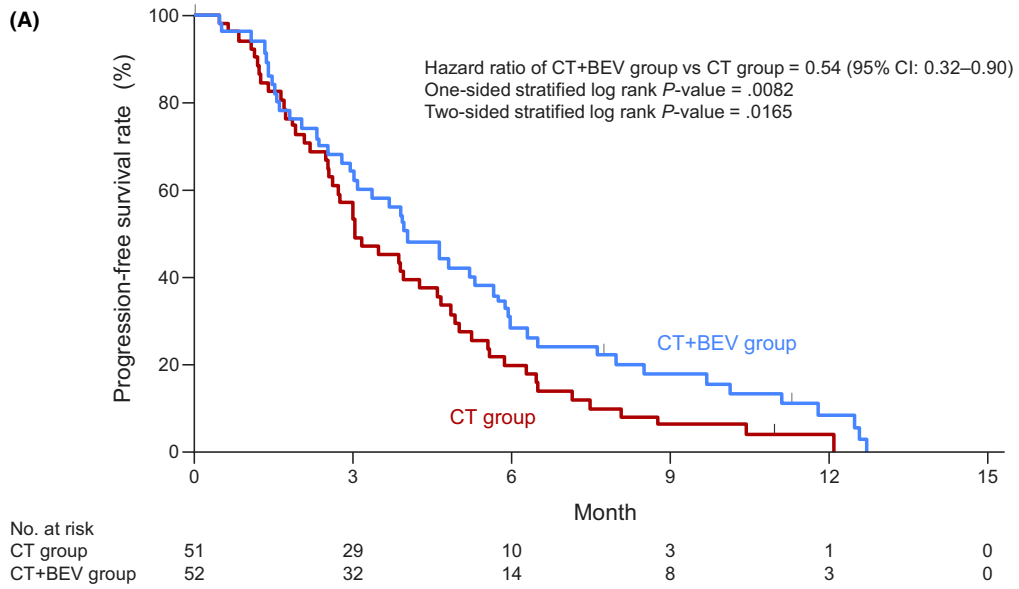
	Chemotherapy group N = 51	Chemotherapy + bevacizumab group N = 52
Age, y	60.7 ± 12.15	60.3 ± 9.71
<65 y	25 (49.0)	33 (63.5)
≥65 y	26 (51.0)	19 (36.5)
ECOG PS		
0	43 (84.3)	43 (82.7)
1	8 (15.7)	7 (13.5)
2	0	0
3	0	0
4	0	0
Missing	0	2 (3.8)
FIGO stage		
I	3 (5.9)	3 (5.8)
II	3 (5.9)	3 (5.8)
III	27 (52.9)	37 (71.2)
IV	18 (35.3)	9 (17.3)
Histological category		
Serous carcinoma	35 (68.6)	29 (55.8)
Clear cell carcinoma	9 (17.6)	7 (13.5)
Endometrioid carcinoma	3 (5.9)	5 (9.6)
Mucinous carcinoma	1 (2.0)	3 (5.8)
Other	3 (5.9)	8 (15.4)
Number of prior regimens		
1 or 2	43 (84.3)	45 (86.5)
≥3	8 (15.7)	7 (13.5)
Platinum-free interval		
During treatment (<28 d)	12 (23.5)	12 (23.1)
28 d to <3 mo	9 (17.6)	11 (21.2)
3 to <6 mo	30 (58.8)	29 (55.8)
Chemotherapy		
Liposomal doxorubicin	21 (41.2)	21 (40.4)
Topotecan	4 (7.8)	4 (7.7)
Paclitaxel	8 (15.7)	8 (15.4)
Gemcitabine	18 (35.3)	19 (36.5)
Presence of ascites	21 (41.2)	18 (34.6)
Maximum tumor diameter, mm	33.1 ± 25.38	29.6 ± 15.91
Patients who received bevacizumab as front-line therapy	25 (49.0)	27 (51.9)
Patients who received bevacizumab for platinum-sensitive ovarian cancer	26 (51.0)	25 (48.1)

Note: Data are n (%) or mean ± standard deviation.

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics.

neutrophil count decreased (n = 1) in the chemotherapy + bevacizumab group; all 3 AEs resolved after appropriate interventions.

AEs leading to discontinuation of chemotherapy are shown in Table 3. AEs leading to discontinuation of bevacizumab were proteinuria (3 events), infections and infestations: other (2 events), and 1 event each of duodenal perforation, thromboembolic event, ileus, small intestinal obstruction, rash maculo-papular, pneumonitis, and pulmonary fibrosis.



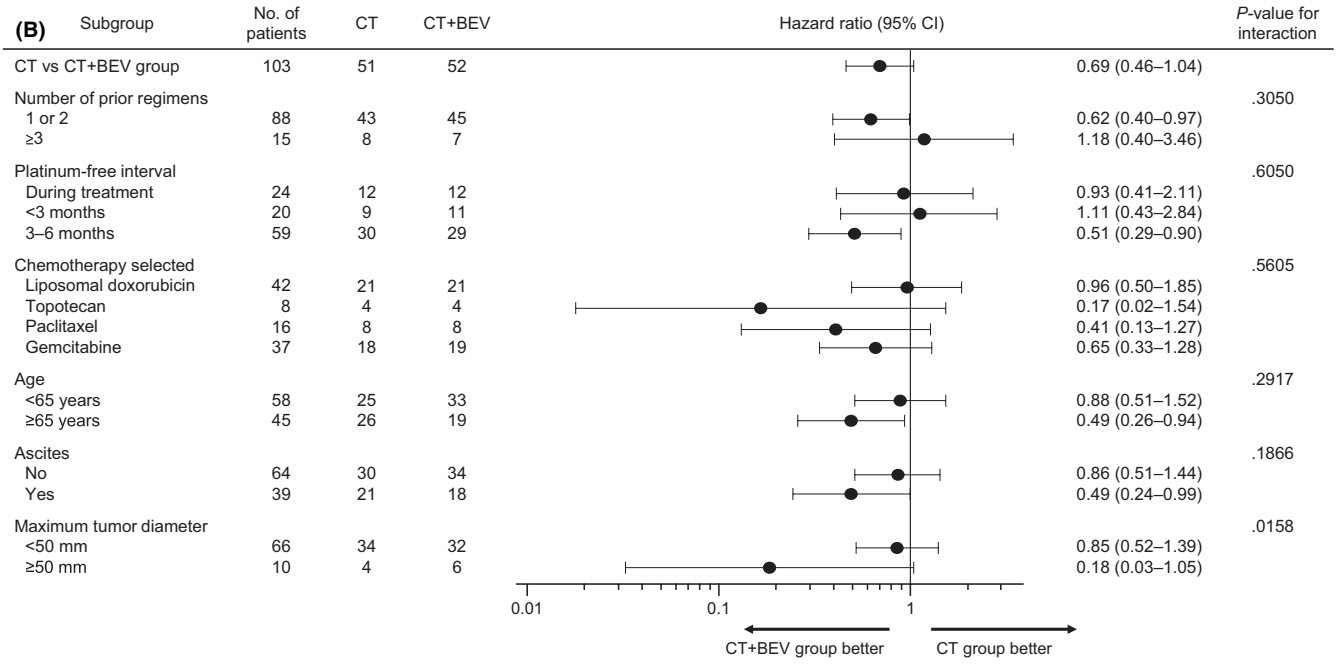
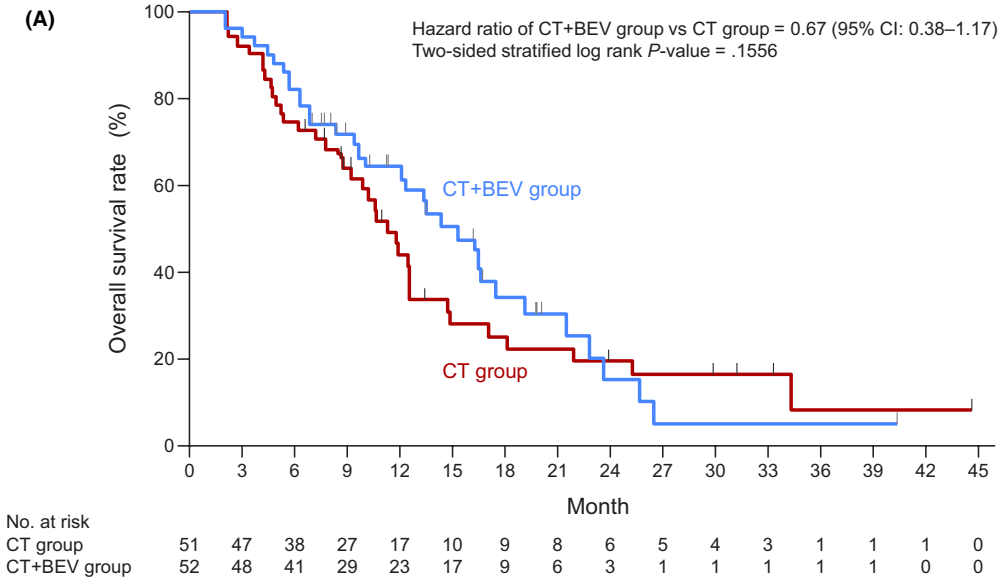


FIGURE 2 Kaplan-Meier curve for investigator-assessed progression-free survival (A) and forest plot of progression-free survival and interaction term test based on a multivariate Cox regression model (B) (intent-to-treat analysis set). BEV, bevacizumab; CI, confidence interval; CT, chemotherapy

4 | DISCUSSION

Overall survival is short in patients with recurrent ovarian cancer, and low response rates are observed with current treatments.[4,5] However, the recent QUADRA trial demonstrated the clinical efficacy of niraparib in patients with recurrent ovarian cancer.[19] Although the trial enrolled a broad population that included platinum-sensitive, platinum-refractory, and platinum-resistance populations, the primary endpoint was overall response in patients who were platinum sensitive. For patients with platinum-resistant and recurrent ovarian cancer, there is a paucity of effective treatment options. Our study differed from the QUADRA trial as the study population was composed entirely of patients with platinum-refractory or platinum-resistant disease.

Previous trials, in various recurrent or metastatic cancer types other than ovarian cancer, have demonstrated the benefit of bevacizumab added to chemotherapy for progressive disease.[11-13] In addition, the increased efficacy of chemotherapy + bevacizumab beyond progressive disease compared with chemotherapy alone was shown in a xenograft model of human ovarian clear cell carcinoma.[20] The AURELIA clinical



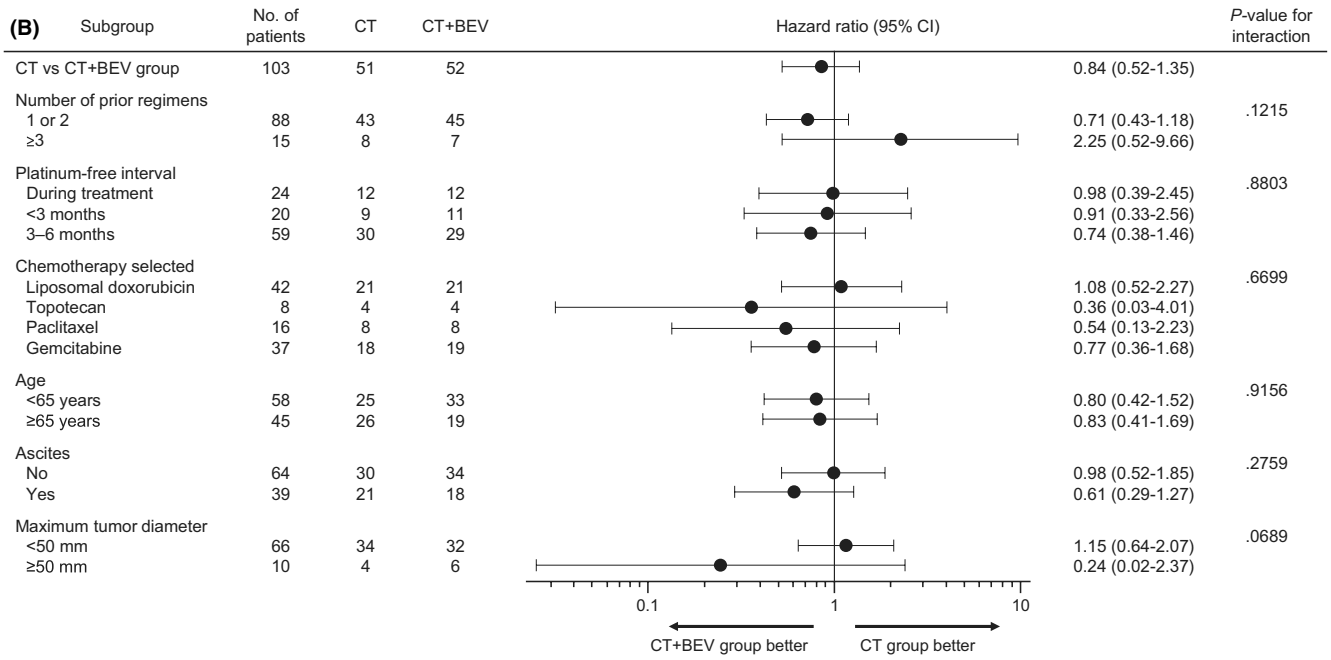


FIGURE 3 Kaplan-Meier curve for overall survival (A) and forest plot of overall survival and interaction term test based on a multivariate Cox regression model (B) (intent-to-treat analysis set). BEV, bevacizumab; CI, confidence interval; CT, chemotherapy

trial previously demonstrated that chemotherapy + bevacizumab was able to significantly improve PFS in patients with platinum-resistant recurrent ovarian cancer not previously treated with bevacizumab.[10] In comparison, our study differs from the AURELIA trial as it includes patients with progressive platinum-resistant and recurrent cancer who had previously received bevacizumab treatment. As such, we describe the efficacy and safety of chemotherapy + bevacizumab in this population and show that this is a treatment option in which none was previously established. Of note, the safety profile in our study is also consistent with that shown in the AURELIA trial.

PFS was 4 mo in the chemotherapy + bevacizumab group in this study compared with 6.7 mo in the AURELIA trial.[10] The reasons for this difference may be due to variations between the 2 studies in patients' baseline characteristics. First, the present study included patients who had received third-line or later-line treatment, while the AURELIA trial excluded such patients. Second, the percentage of patients with a platinum-free interval of less than 3 mo was 40%-45% in the present study and approximately 30% in the AURELIA trial. Third, regarding histological categories, the percentage of patients with serous carcinoma, for which chemotherapy is considered to be effective, was 55.8% in this study, compared with 85% in the AURELIA trial. Finally, approximately 30% of attending physicians selected paclitaxel for combination treatment with bevacizumab in the AURELIA trial while approximately 15% in our study selected

TABLE 2 Summary of adverse events and treatment-related adverse events

	Chemotherapy group (N = 50)	Chemotherapy + bevacizumab group (N = 51)
Any AEs	50 (100)	50 (98.0)
Serious AEs	8 (16.0)	12 (23.5)
AEs leading to treatment discontinuation	2 (4.0)	12 (23.5)
AEs of grade ≥3	23 (46.0)	30 (58.8)
Any treatment-related AEs	48 (96.0)	49 (96.1)
Serious treatment-related AEs		
Related to chemotherapy or BEV (or related to both)	3 (6.0)	8 (15.7)
Related to chemotherapy	3 (6.0)	6 (11.8)
Related to BEV	0	4 (7.8)
Treatment-related AEs grade ≥3	21 (42.0)	28 (54.9)
Grade ≥3 treatment-related AEs occurring in ≥3% of patients (preferred term)		
Neutrophil count decreased	16 (32.0)	19 (37.3)
Platelet count decreased	7 (14.0)	5 (9.8)
Anemia	4 (8.0)	5 (9.8)
Anorexia	1 (2.0)	3 (5.9)
Febrile neutropenia	3 (6.0)	1 (2.0)
Palmar-plantar erythrodysesthesia syndrome	2 (4.0)	0
Infections and infestations – other	0	3 (5.9)
Proteinuria	0	3 (5.9)
Hypertension	0	2 (3.9)
Mucositis oral	0	2 (3.9)
Hypoalbuminemia	0	2 (3.9)

Note: Data are n (%).

Abbreviations: AE, adverse event; BEV, bevacizumab.

TABLE 3 Adverse events leading to discontinuation of chemotherapy

	Chemotherapy group (N = 50)	Chemotherapy + bevacizumab group (N = 51)
Ileus	1 (2.0)	1 (2.0)
Pneumonitis	1 (2.0)	1 (2.0)
Infections and infestations – other	0	2 (3.9)
Duodenal perforation	0	1 (2.0)
Thromboembolic event	0	1 (2.0)
Small intestinal obstruction	0	1 (2.0)
Rash maculopapular	0	1 (2.0)
Platelet count decreased	0	1 (2.0)
Pulmonary fibrosis	0	1 (2.0)

Note: Data are n (%).

paclitaxel for combination treatment. This is important because, in an exploratory analysis of the AURELIA trial, it was shown that for the weekly paclitaxel cohort there was a more pronounced treatment effect on ORR, PFS, and OS compared with the PLD or topotecan treatment cohorts.[21]

In the present study, interactions with treatment allocation were detected for the maximum tumor diameter ($P = .0158$) and presence of ascites ($P = .1866$). Although there was no significant difference between the chemotherapy group and chemotherapy + bevacizumab group in terms of the *P*-value for the presence of ascites,

this finding suggests that the addition of bevacizumab is effective in cases with tumor diameter ≥50 mm and cases with ascites.

Our results demonstrated that OS was longer in the chemotherapy + bevacizumab group (15.3 mo) than in the chemotherapy group (11.3 mo; $P = .1556$). Although no statistically significant improvement in OS was shown, we considered that the endpoint would have been met with a larger sample size. These findings are consistent with the results of the AURELIA trial that reported no statistically significant difference in OS between the regimens (median OS 16.6 mo in the chemotherapy + bevacizumab group and 13.3 mo in the chemotherapy group; unstratified log-rank $P < .174$).[10] When evaluating the HR of OS by subgroups in the present study, increased efficacy was generally shown in the chemotherapy + bevacizumab group.

ORR in this study was approximately twice as high in the chemotherapy + bevacizumab group (25.0%) than in the chemotherapy group (13.7%; $P = .0599$). This finding supports the additive effect of bevacizumab in single-agent chemotherapy. Similarly, the MITO16B/MaNGO-OV2B/ENGOT-OV17 study reported a higher ORR with chemotherapy + bevacizumab vs chemotherapy (69.2% vs 49.7%, $P = .001$).[14]

In a previous study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer, gastrointestinal perforation occurred in 23.8% of patients previously treated with more than 3 regimens,[22] which suggests that this AE may warrant specific monitoring in patients with ovarian cancer receiving multiple bevacizumab treatment regimens. In the present study, 1 patient (2.0%) in the chemotherapy + bevacizumab group presented with a grade ≥3 duodenal perforation, and this patient had received 2 previous treatment regimens. No gastrointestinal perforation was observed in those previously treated with 3 or more regimens, although it should be noted that only 7 patients in the chemotherapy + bevacizumab group had received 3 or more prior regimens. We considered that the scarcity of gastrointestinal perforation in our study was due to the strict exclusion of patients with 4 or more prior regimens and of those who had bowel obstruction or bowel involvement, as these patients were considered to be at greater risk of this AE. Therefore, we considered that treatment with bevacizumab can be safely continued in patients who have received prior treatment with bevacizumab, without the occurrence of gastrointestinal perforation, as long as potential risk factors are taken into consideration.

AEs specific to bevacizumab observed in this study did not notably differ from those in the AURELIA trial,[10] suggesting that tolerability is favorable even in patients who received prior treatment with bevacizumab. The incidences of both hypertension and proteinuria of grade 3 or higher were similar between the AURELIA trial and the present study (hypertension, 7.3% vs 5.9%; proteinuria, 1.7% vs 5.9%, respectively). Furthermore, even though patients in our study received continuous treatment with bevacizumab, despite prior treatment with this agent, the incidences of hypertension and proteinuria were lower than those reported in a previous study of bevacizumab conducted in Japanese patients (23.2% and 12.6%, respectively).[23] This finding indicates the possibility that patients who had not experienced these AEs during the prior treatment were enrolled.

To our knowledge, this is the first study to investigate continuing bevacizumab beyond progressive disease in patients with platinum-resistant recurrent ovarian cancer who show a limited response to treatment. While our data suggest that bevacizumab plus chemotherapy may be a new treatment option for this patient population, we acknowledge that the study has some limitations, particularly those inherent to the open-label design. In addition, the results have limited generalizability, because only Japanese patients were included and because of the relatively small size of the study, which was expected, due to the relative rarity of platinum-resistant recurrent ovarian cancer in patients who received prior treatment with bevacizumab. Nonetheless, our data provide information relevant to the management of this disease, and our findings should be confirmed in a larger, more geographically inclusive, phase III study.

The results of this phase II study demonstrated the efficacy and manageable toxicity of continuing bevacizumab beyond progressive disease in patients with platinum-resistant recurrent ovarian cancer previously treated with bevacizumab for front-line or platinum-sensitive recurrent ovarian cancer. However, although an improvement in PFS was observed, further verification is required.

ACKNOWLEDGMENTS

This study was funded by Chugai Pharmaceutical Co., Ltd. The authors wish to thank all members of the Japanese Gynecologic Oncology Group. The authors also wish to thank Michelle Belanger, MD, of Edanz (www.edanz.com), for providing medical writing assistance, which was funded by Chugai Pharmaceutical Co., Ltd. through EMC KK, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). We thank the women who participated in this study and their families, Tetsutaro Hamano and the staff of Kitasato Academic Research Organization (the data and statistical analysis center for JGOG3023), and the participating JGOG member institutions.

DISCLOSURE

Tadahiro Shoji, Masakazu Abe, Takayuki Nagasawa, Tetsuro Oishi, Masahiko Mori, Yuki Inokuchi, Shoji Kamiura, and Toru Sugiyama have nothing to declare. Takayuki Enomoto has received honoraria from AstraZeneca, MSD, and Chugai Pharmaceutical; and grant funding from Chugai Pharmaceutical. Aikou Okamoto has received honoraria from AstraZeneca and Takeda Pharmaceutical; grant funding from CMIC, Kaken Pharmaceutical, Daiichi Sankyo, and Mochida Pharmaceutical. Satoru Nagase has received lecture fees from Chugai Pharmaceutical and AstraZeneca. Shinichi Komiyama has received honoraria from Chugai Pharmaceutical and AstraZeneca. Nobuhiro Takeshima has received honoraria from AstraZeneca.

ORCID

Tadahiro Shoji https://orcid.org/0000-0002-9022-3333
Shinichi Komiyama https://orcid.org/0000-0003-0420-5700

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2017;67:7-30.
2. Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol*. 2009;27:1419-1425.
3. Pignata S, Lorusso D, Scambia G, et al. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): a randomised, open-label, phase 2 trial. *Lancet Oncol*. 2015;16:561-568.
4. Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24 (Suppl 6):vi24-vi32.
5. Luvero D, Milani A, Ledermann JA. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. *Ther Adv Med Oncol*. 2014;6(5):229-239.
6. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011;365:2473-2483.
7. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med*. 2011;365:2484-2496.
8. Aghajanian C, Blank SV, Goff BA, et al. 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. *J Clin Oncol*. 2012;30:2039-2045.
9. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18:779-791.
10. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32:1302-1308.
11. von Minckwitz G, Puglisi F, Cortes J, et al. Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15:1269-1278.
12. Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). *J Clin Oncol*. 2008;26:5326-5334.
13. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol*. 2013;14:29-37.
14. Pignata S, Lorusso D, Joly F, et al. Carboplatin-based doublet plus bevacizumab beyond progression versus carboplatin-based doublet alone in patients with platinum-sensitive ovarian cancer: a randomised, phase 3 trial. *Lancet Oncol*. 2021;22:267-276.
15. Shoji T, Komiyama S, Kigawa J, et al. An open-label, randomized, phase II trial evaluating the efficacy and safety of standard of care with or without bevacizumab in platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer patients previously treated with bevacizumab for front-line or platinum-sensitive ovarian cancer: rationale, design, and methods of the Japanese Gynecologic Oncology Group study JGOG3023. *BMC Cancer*. 2018;18:771.
16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.
17. Rustin GJ, Vergote I, Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *Int J Gynecol Cancer*. 2011;21:419-423.
18. Japan Clinical Oncology Group. Common Toxicity Criteria for Adverse Events version 4.0 Japanese Translation (CTCAE-JCOG). http://www.jcog.jp/doctor/tool/ctcaev4.html. Accessed March 23, 2000.
19. Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20(5):636-648.
20. Ishikura N, Yorozu K, Kurasawa M, et al. Sustained effect of continuous treatment with bevacizumab following bevacizumab in combination with chemotherapy in a human ovarian clear cell carcinoma xenograft model. *Oncol Rep*. 2019;42:1057-1065.
21. Poveda AM, Selle F, Hilpert F, et al. 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. *J Clin Oncol*. 2015;33:3836-3838.
22. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol*. 2007;25:5180-5186.
23. Komiyama S, Kato K, Inokuchi Y, et al. Bevacizumab combined with platinum-taxane chemotherapy as first-line treatment for advanced ovarian cancer: a prospective observational study of safety and efficacy in Japanese patients (JGOG3022 trial). *Int J Clin Oncol*. 2019;24:103-114.

How to cite this article: Shoji T, Enomoto T, Abe M, et al. Efficacy and safety of standard of care with/without bevacizumab for platinum-resistant ovarian/fallopian tube/peritoneal cancer previously treated with bevacizumab: The Japanese Gynecologic Oncology Group study JGOG3023. *Cancer Sci*. 2022;113:240–250. https://doi.org/10.1111/cas.15185