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Efficacy and Safety of Bevacizumab-Containing Therapy in Newly Diagnosed Ovarian Cancer

ROSiA Single-Arm Phase 3B Study

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Objective: The aim of this study was to assess the safety and efficacy of extending bevacizumab therapy beyond 15 months in nonprogressive ovarian cancer.

Patients and Methods: In this multinational prospective single-arm study (ClinicalTrials.gov NCT01239732), eligible patients had International Federation of Gynecology and Obstetrics stage IIB to IV or grade 3 stage I to IIA ovarian cancer without clinical signs or symptoms of gastrointestinal obstruction or history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the preceding 6 months. Prior neoadjuvant

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chemotherapy was permitted. After debulking surgery, patients received bevacizumab 15 (or 7.5) mg/kg every 3 weeks (q3w) with 4 to 8 cycles of paclitaxel (investigator's choice of 175 mg/m² q3w or 80 mg/m² weekly) plus carboplatin AUC 5 to 6 q3w. Single-agent bevacizumab was continued until progression or for up to 24 months. The primary end point was safety.

Results: Between December 2010 and May 2012, 1021 patients from 35 countries began study treatment. Bevacizumab was administered at 15 mg/kg in 89% of patients and for more than 15 months in 53%. Median follow-up duration was 32 months (range, 1–50 months). The most common all-grade adverse events were hypertension (55% of patients), neutropenia (49%), and alopecia (43%). The most common grade 3 or higher-grade adverse events were neutropenia (27%) and hypertension (25%). Bevacizumab was discontinued because of proteinuria in 5% of patients and hypertension in 3%. Median progression-free survival (PFS) was 25.5 months (95% confidence interval, 23.7–27.6 months).

Conclusion: Extended bevacizumab demonstrated increased incidences of proteinuria and hypertension compared with 12 or 15 months of bevacizumab in previous trials, but these rarely led to bevacizumab discontinuation. Median PFS is the longest reported for frontline bevacizumab-containing therapy. The longer bevacizumab duration beyond 15 months in this study may improve PFS without substantially compromising safety.

Key Words: Bevacizumab, Ovarian cancer, Angiogenesis, Frontline, Maintenance

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Ovarian cancer is the sixth most common in incidence and the fifth most common cause of cancer death in women in Europe.¹ In many countries, bevacizumab given concurrently with chemotherapy and then continued as a single agent represents a frontline treatment option for women with stage IIIB to IV disease. The benefit of combining bevacizumab with standard chemotherapy was demonstrated in 2 randomized phase 3 trials: GOG-0218 (evaluating bevacizumab 15 mg/kg every 3 weeks [q3w] for up to 15 months)² and ICON7 (evaluating bevacizumab 7.5 mg/kg q3w for up to 12 months).³ Both trials met their primary objective, significantly improving progression-free survival (PFS) with bevacizumab added to standard chemotherapy.

The more pronounced PFS benefit from bevacizumab in GOG-0218 than ICON7, together with subgroup analyses according to stage and residual disease,^{4,5} led to 2 major hypotheses. First, patients with more advanced disease or at high risk of progression may derive greater benefit from bevacizumab. Second, the effect of bevacizumab on PFS may be enhanced by extending bevacizumab exposure. In ICON7, the PFS difference between the bevacizumab- and non-bevacizumab-containing treatment arms peaked at 12 months, corresponding to the end of bevacizumab treatment. Thereafter, the PFS difference between treatment arms diminished, although the bevacizumab effect on overall survival (OS) in the subgroup considered at high risk of progression was sustained beyond the duration of bevacizumab exposure. Further support for increasing the duration of bevacizumab comes from preclinical models suggesting that

maintenance bevacizumab may prolong OS⁶ and trials evaluating bevacizumab in the recurrent setting in which bevacizumab was continued until disease progression and showed a magnitude of benefit larger than in the frontline trials using a fixed treatment duration.^{7,8}

The primary aim of the single-arm ROSiA study was to explore the safety of extending the duration of single-agent bevacizumab after concurrent administration with chemotherapy for newly diagnosed ovarian cancer.

METHODS

Study Design and Patients

Generally, eligibility criteria were designed to recruit a patient population similar to that enrolled in ICON7. Patients had to be aged 18 years or older with Eastern Cooperative Oncology Group performance status 0 to 2. Eligible patients had histologically confirmed epithelial ovarian carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma of International Federation of Gynecology and Obstetrics (FIGO) stage IIB to IV (any grade) or stage I to IIA (grade 3), or clear cell carcinoma, or carcinosarcoma. Patients should have already undergone maximal surgical debulking unless they had inoperable stage III or IV disease. Unlike ICON7, patients could be enrolled after neoadjuvant chemotherapy and interval debulking surgery, with bevacizumab initiated after surgery.

Key exclusion criteria included the following: uncontrolled hypertension; clinically significant cardiovascular disease;

TABLE 1. Baseline characteristics (n = 1021)

Characteristic	No. of Patients (%)
Age, years	
Median (range)	56 (20–82)
Age ≥65	258 (25.3)
Age ≥70	121 (11.9)
ECOG performance status*	
0	706 (69.1)
1	282 (27.6)
2	25 (2.4)
Origin of cancer†	
Ovary	930 (91.1)
Fallopian tube	41 (4.0)
Primary peritoneal	48 (4.7)
Other	2 (0.2)
Ascites at baseline	191 (18.7)
Hypertension at baseline	336 (32.9)
Proteinuria at baseline	19 (1.9)
Prior neoadjuvant chemotherapy with interval debulking surgery	206 (20.2)
Stage IIIB–IV	785 (76.9)
Measurable disease	421 (41.2)
Histologic classification‡	
Serous	750 (73.5)
Endometrioid	90 (8.8)
Clear cell	68 (6.7)
Mucinous	23 (2.3)
Mixed	65 (6.4)
Adenocarcinoma NOS	88 (8.6)
Other	48 (4.7)
Grade	
1	75 (7.3)
2	193 (18.9)
3	703 (68.9)
Missing	50 (4.9)
FIGO stage	
I/IIA	88 (8.6)
IIB/IIC	75 (7.3)
II (not further classified)	4 (0.4)
III (not further classified)	29 (2.8)
IIIA	40 (3.9)
IIIB	60 (5.9)
IIIC	485 (47.5)
IV	240 (23.5)
Debulking surgery performed	967 (94.7)
Median time (range) from surgery to start of bevacizumab, weeks	6.1 (2.3–351.3)

TABLE 1. (Continued)

Characteristic	No. of Patients (%)
Outcome of debulking surgery‡	
> 1 cm	328 (33.9)
≤ 1 cm	639 (66.1)
Macroscopic (1–10 mm)	200 (20.7)
Microscopic (<1 mm)	286 (29.6)
Unknown	152 (15.7)
Missing	1 (0.1)
High risk of recurrence (MRC definition§)	468 (45.8)
Bowel resection	
Small	53 (5.2)
Large	92 (9.0)
Both	18 (1.8)

*Missing in 8 patients (0.8%).

†Multiple entries possible.

‡Percentages calculated using a denominator of 967 (patients with debulking surgery).

§FIGO stage III with >1-cm residuum, FIGO stage IV, or no debulking surgery.

ECOG, Eastern Cooperative Oncology Group; MRC, Medical Research Council; NOS, not otherwise specified.

preexisting grade 2 or higher-grade peripheral neuropathy; active gastrointestinal bleeding; clinical signs or symptoms of gastrointestinal obstruction requiring parenteral hydration and/or nutrition; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the preceding 6 months; serious or nonhealing wound; history or evidence of grade 1 or higher-grade arterial thromboembolic event or grade 3 or higher-grade venous thromboembolic event within the 6 months preceding enrollment; and major surgery within 28 days before the first bevacizumab dose.

All patients provided written informed consent before any study-specific procedures. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol and all amendments were approved by an institutional review board for each site. Bevacizumab is not approved by the US Food and Drug Administration as frontline treatment for ovarian cancer.

Procedures

After primary or interval debulking surgery, patients received bevacizumab 15 mg/kg (or 7.5 mg/kg at the investigator's discretion following a protocol amendment after the release of the ICON7 results) q3w in combination with 4 to 8 cycles of carboplatin and paclitaxel. Carboplatin was given at area under the curve 5 to 6 q3w and could be replaced with cisplatin in patients with hypersensitivity to carboplatin. Paclitaxel was administered at either 175 mg/m² q3w or 80 mg/m² weekly (investigator's choice); switching dosing schedule during the study was not permitted.

After chemotherapy discontinuation, single-agent bevacizumab was continued until disease progression or for up to

24 months (36 cycles). Bevacizumab could be continued beyond 36 cycles after consultation with the principal investigator if the treating physician considered this to be in the patient's best interests and there was neither evidence of disease progression nor a contraindication to bevacizumab.

Outcomes

The primary end point was safety. Adverse events (AEs) were graded using Common Terminology Criteria for Adverse Events (version 4.03). Secondary end points included PFS (Response Evaluation Criteria in Solid Tumors [RECIST], version 1.0; or symptomatic deterioration), objective response rate (RECIST, version 1.0), duration of response, and OS. Tumors were assessed radiologically after cycles 3 and 6, then every 6 cycles during bevacizumab therapy, and at the time of bevacizumab discontinuation. Thereafter, tumors were assessed every 26 weeks until disease progression. Cancer antigen (CA)-125 measurements were not used to determine disease progression for the calculation of PFS, and CA-125 measurement was not required after disease progression. Translational research was an exploratory objective but will be reported separately. An independent data monitoring committee reviewed safety data at regular intervals to ensure patient safety and compliance with the protocol.

Statistical Analysis

Efficacy and safety analyses were based on the population of patients who received at least 1 bevacizumab dose. Safety analyses included all AEs occurring between the first dose of study treatment and 30 days after the last dose (or until 26 weeks after the last dose for AEs considered to be related to study treatment).

Progression-free survival was defined as the interval between the first dose of any study treatment and the first documented disease progression or death, whichever occurred earlier. In patients who were alive without disease progression at the time of study completion or who withdrew from the study or were lost to follow-up without documented disease progression, data were censored at the date of the last available tumor assessment. Overall survival was defined as the interval between the first dose of any study treatment and death from any cause; data for patients who were still alive were censored at the date the patient was last known to be alive. Progression-free survival and OS were estimated using Kaplan-Meier methodology.

Response and duration of response were assessed in patients with measurable disease at baseline. The proportion of patients achieving a response is presented with 2-sided 95% Pearson-Clopper confidence intervals (CIs). Statistical analyses were done using SAS (version 9.1.3; SAS Institute Inc, Cary, NC).

RESULTS

Patient Population and Treatment Exposure

Between December 17, 2010, and May 10, 2012, 1021 patients from 35 countries began treatment in ROSiA (Appendix 1, <http://links.lww.com/IGC/A416>). Table 1 summarizes baseline characteristics. In most patients, paclitaxel was

initiated with a q3w schedule and bevacizumab was given at a dose of 15 mg/kg q3w (Table 2). The first bevacizumab cycle was omitted in 201 patients because of the short interval since previous surgery.

Data cutoff for this final analysis was December 7, 2014; the median duration of follow-up was 32 months (range, 0.7–49.5 months). Bevacizumab was administered for more than 1 year in 632 (62%) of 1021 patients, more than 15 months in 537 patients (53%), and more than 2 years in 298 patients (29%) (Fig. 1, Table 2).

Bevacizumab was discontinued because of disease progression in 332 patients (33%), unacceptable toxicity in

TABLE 2. Treatment exposure

Treatment Exposure	Safety Population
	(n = 1021)
	No. of Patients (%)
Bevacizumab	
Initial dose,* mg/kg	
7.5	106 (10.4)
15	909 (89.0)
Median No. of bevacizumab cycles (range)	23 (1–61)
Median duration of bevacizumab, months (range)	15.5 (<0.1–43.2)
Received bevacizumab for >12 months	632 (61.9)
Received bevacizumab for >15 months	537 (52.6)
Received bevacizumab for >24 months	298 (29.2)
Delay or modification	755 (73.9)
Delay or modification for AEs	597 (58.5)
Paclitaxel	
Weekly schedule	71 (7.0)†
q3w schedule	950 (93.0)
Median No. of paclitaxel cycles (range)	6 (1–8)
Median duration of paclitaxel, (range), months	3.5 (<0.1–28.1)
Delay or modification	545 (53.4)
Delay or modification for AEs	489 (47.9)
Carboplatin	
Median No. of carboplatin cycles (range)	6 (1–8)
Median duration of carboplatin, months (range)	3.5 (<0.1–28.1)
Delay or modification	546 (53.5)
Delay or modification for AEs	481 (47.1)

*Missing in 6 patients (0.6%).

†Three of these patients subsequently switched to the q3w schedule.

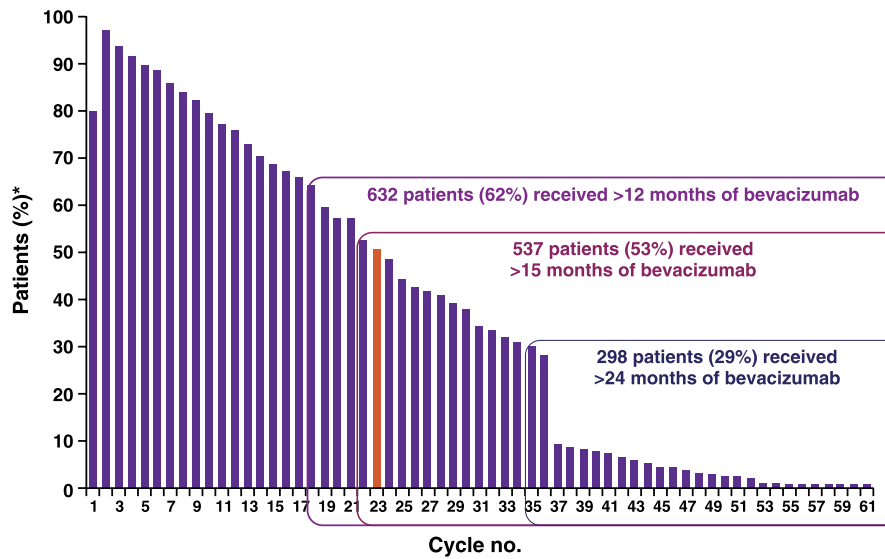


FIGURE 1. Bevacizumab exposure by cycle. *Denominator at each cycle is 1021.

TABLE 3. Grade ≥3 AEs of special interest overall and according to time of first onset (up to or after cycle 22)

Adverse Event	No. of Patients (%)									
	Entire Study Period (n = 1021)*				Cycles 0–22 (n = 1021)*			Cycle 23 Onward (n = 528)*†		
	Grade ≥3	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Any AE of special interest	549 (53.8)	404 (39.6)	139 (13.6)	6 (0.6)	379 (37.1)	136 (13.3)	5 (0.5)	64 (12.1)	3 (0.6)	1 (0.2)
Neutropenia and associated complications	299 (29.3)	186 (18.2)	112 (11.0)	1 (0.1)	186 (18.2)	112 (11.0)	1 (0.1)	0	0	0
Febrile neutropenia	30 (2.9)	23 (2.3)	6 (0.6)	1 (0.1)	23 (2.3)	6 (0.6)	1 (0.1)	0	0	0
Hypertension	252 (24.7)	246 (24.1)	6 (0.6)	0	218 (21.4)	5 (0.5)	0	49 (9.3)	1 (0.2)	0
Thrombocytopenia	100 (9.8)	83 (8.1)	17 (1.7)	0	83 (8.1)	17 (1.7)	0	0	0	0
Proteinuria	39 (3.8)	39 (3.8)	0	0	29 (2.8)	0	0	12 (2.3)	0	0
Thromboembolic events	30 (2.9)	19 (1.9)	8 (0.8)	3 (0.3)	19 (1.9)	6 (0.6)	2 (0.2)	0	2 (0.4)	1 (0.2)
Gastrointestinal perforation	14 (1.4)	9 (0.9)	4 (0.4)	1 (0.1)	8 (0.8)	4 (0.4)	1 (0.1)	1 (0.2)	0	0
Bleeding	8 (0.8)	5 (0.5)	1 (0.1)	2 (0.2)	4 (0.4)	1 (0.1)	2 (0.2)	1 (0.2)	0	0
Wound-healing complication	4 (0.4)	4 (0.4)	0	0	3 (0.3)	0	0	1 (0.2)	0	0
Fistula/abscess	4 (0.4)	3 (0.3)	1 (0.1)	0	3 (0.3)	1 (0.1)	0	0	0	0
Congestive heart failure	2 (0.2)	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	0	0	0
Posterior reversible encephalopathy syndrome	1 (0.1)	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0

*Worst grade across the stated period; AEs by treatment period may add up to more than the total across the entire study period.
 †Percentages calculated using a denominator of 528.

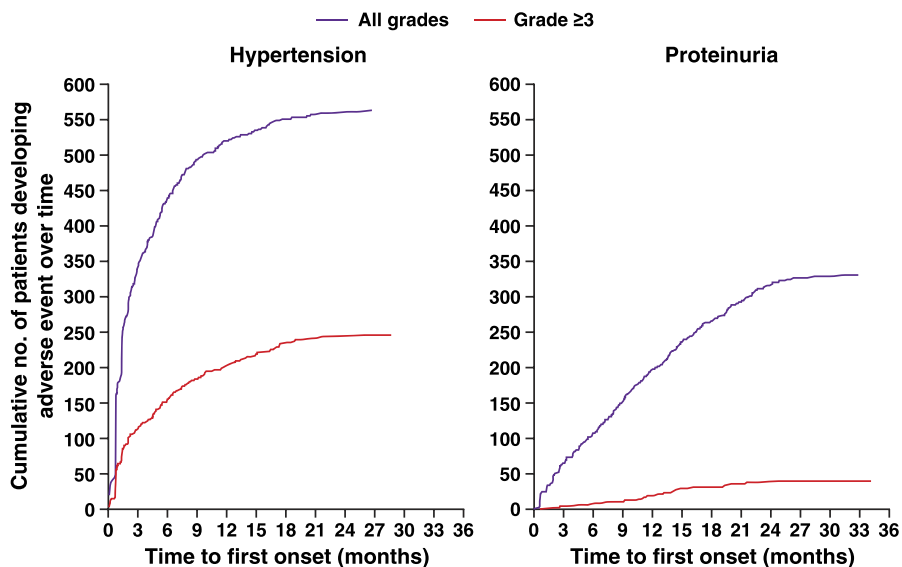


FIGURE 2. Cumulative number of patients developing hypertension or proteinuria over time.

176 patients (17% [proteinuria in 55 patients; hypertension in 30 patients]), and consent withdrawal in 111 patients (11%). In 145 patients, study therapy was discontinued before the maintenance bevacizumab phase; the remaining 876 patients received at least 1 cycle of maintenance bevacizumab. Among the 176 patients who discontinued bevacizumab because of unacceptable toxicity, the median time to discontinuation was 9.9 months (range, 0–35 months); the median time to bevacizumab discontinuation because of consent withdrawal was 10.1 months (range, 0–28 months).

Safety

The most common all-grade AEs were hypertension (55%), neutropenia (49%), and alopecia (43%) (Appendix Table A1, <http://links.lww.com/IGC/A417>). Grade ≥ 3 AEs occurred in 683 patients (67%): grade 3 in 521 (51%), grade 4 in 150 (15%), and grade 5 in 12 patients (1.2%). Four of the fatal AEs occurred during concurrent chemotherapy (1 case each of peritoneal abscess, pneumonia, febrile neutropenia with disseminated intravascular coagulation, and pulmonary embolism), and 6 occurred during the maintenance bevacizumab phase (ileus associated with ovarian cancer progression, general physical health deterioration, hypovolemic shock, pleural effusion with congestive heart failure, unexplained death, and myocardial infarction). The 2 remaining deaths occurred 45 and 61 days after discontinuation of study therapy (intracranial hemorrhage; septic shock after surgery for jejunal perforation, considered by the investigator possibly due to disease progression or to bevacizumab).

The most common grade 3 or higher-grade AEs were neutropenia (reported as a clinical AE [27%]) and hypertension (25%). Table 3 shows grade 3 or higher-grade AEs of special interest for bevacizumab. Grade 3 proteinuria occurred in 4% of patients (no grade 4); 1.4% experienced grade 3 or higher-grade gastrointestinal perforation. Bevacizumab was discontinued owing to proteinuria in 55 (5%) of 1021 patients (including some who discontinued because of

persistent grade 2 proteinuria), hypertension in 30 patients (3%), thrombocytopenia in 3 patients (0.3%), and neutropenia in 1 patient (0.1%).

Further analyses indicated that for most AEs of special interest, especially hematologic toxicities, the first occurrence was during the concurrent chemotherapy phase (Appendix Table A2, <http://links.lww.com/IGC/A417>). The first onset of grade 3 or higher-grade neutropenia and associated complications occurred during the concurrent chemotherapy phase in 293 patients (29%) and during the single-agent bevacizumab phase in 11 patients (1%). Later onset of AEs of special interest (during the single-agent bevacizumab maintenance phase) was infrequent. The main exceptions were hypertension and proteinuria, which in some patients appeared only after more prolonged bevacizumab exposure, and gastrointestinal perforation, which appeared with a steady but low incidence across all study periods. First onset of thromboembolic events was more common during the concurrent phase, but some new cases appeared during the maintenance and follow-up phases.

Analyses according to appearance before versus after 22 cycles (corresponding to the maximum permitted 15-month bevacizumab duration specified in the European label) showed a similar pattern (Table 3), except that only 1 case of gastrointestinal perforation (grade 3) occurred after cycle 22, with all remaining cases (1.3% of patients) occurring within the first 22 cycles. In addition, first onset of a thromboembolic event was after cycle 22 in 0.6% of patients reaching this time point versus 2.6% of patients within the first 22 cycles. Appendix Table A3, <http://links.lww.com/IGC/A417> shows similar analyses in the subgroup of patients with stage IIIB to IV disease.

To explore the patterns of onset of hypertension and proteinuria further, we plotted the cumulative number of patients with these events over time (Fig. 2). Typically, hypertension first appeared during earlier bevacizumab cycles. Hypertension occurred before month 6 of bevacizumab

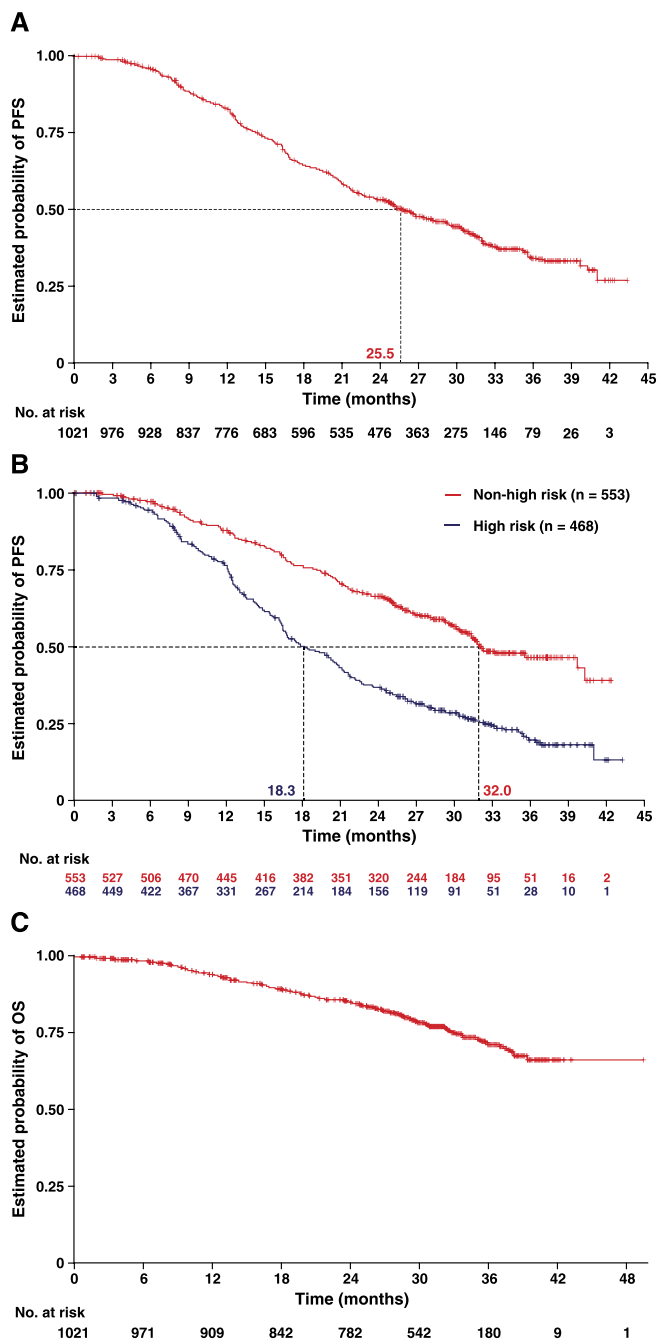


FIGURE 3. Efficacy: PFS in the overall population (A); PFS according to risk status (B); OS (C). High risk: FIGO stage III and greater than 1-cm residual disease or any FIGO stage IV or no debulking surgery.

exposure in 433 (77%) of 563 patients experiencing this AE, with a median time to onset of 2.1 months (range, 0–28 months). Grade 3 or higher-grade hypertension occurred before month 6 of bevacizumab exposure in 158 (63%) of 252 patients developing this AE. In contrast, proteinuria onset showed a more linear relationship between first onset and duration of exposure for the first 24 months.

Efficacy

At the time of database lock, PFS events had been recorded in 558 (55%) of 1021 patients. In the overall population, median PFS was 25.5 months (95% CI, 23.7–27.6 months) (Fig. 3A). The 1-year PFS rate was 82.6% (95% CI, 80.0%–84.8%), and the 2-year PFS rate was 53.0% (95% CI, 49.7%–56.1%). In the subgroup of 468 patients with FIGO stage III and residual disease greater than 1 cm, FIGO stage IV, or no debulking surgery (corresponding to the Medical Research Council definition of “high risk” used in ICON7), median PFS was 18.3 months (95% CI, 16.8–20.6 months) (Fig. 3B). In the converse subgroup of patients with non-high-risk disease, median PFS was 32.0 months (95% CI, 30.9–40.2 months). Among the subgroup of 785 patients with stage IIIB to IV ovarian cancer (the approved frontline indication for bevacizumab in Europe and many other countries), median PFS was 21.6 months (95% CI, 20.6–23.0 months). Table 4 summarizes additional subgroup analyses of PFS.

An objective response was recorded in 306 of the 421 patients with measurable disease at baseline, giving an overall response rate of 73% (95% CI, 68%–77%). This included complete responses in 104 (25%) of 421 patients (95% CI, 21%–29%). The median duration of response in the 306 responding patients was 18.2 months (95% CI, 16.6–19.6 months).

Overall survival data are immature; 235 (23%) of 1021 patients had died at the time of database lock (Fig. 3C). The 1-year OS rate was 94% (95% CI, 93%–96%), and the 2-year OS rate was 85% (95% CI, 83%–87%). Most deaths (218 [93%] of 235 deaths; 21% of the 1021 patients in the study population) were from disease progression.

DISCUSSION

In this large global study evaluating the safety of extended-duration frontline bevacizumab-containing therapy for ovarian cancer, the median duration of bevacizumab exposure was 15.5 months, and 29% of patients continued bevacizumab for more than 2 years. The most common reason for bevacizumab discontinuation was disease progression. The safety profile was generally consistent with experience from the 2 randomized phase 3 trials evaluating shorter durations of bevacizumab,^{2,3} except for increased incidences of proteinuria and hypertension, and an increased incidence of neutropenia compared with ICON7 (but not GOG-0218). Gastrointestinal perforation was relatively infrequent; the 1.3% incidence of grade 3 or higher-grade gastrointestinal perforation is similar to previous reports in this setting. Most AEs occurred during early cycles, when bevacizumab was given concurrently with chemotherapy. Relatively few new AEs occurred during the single-agent bevacizumab maintenance phase, the main exceptions being hypertension and proteinuria.

To gain an impression of the impact on safety of prolonging bevacizumab therapy, we considered the safety results in the context of previous data from randomized phase 3 trials. As the ROSiA study was designed to enroll a patient population similar to that treated in ICON7, interpretation of the results in the context of ICON7 results seems reasonable, although the bevacizumab dose more closely resembles that in

TABLE 4. Subgroup analyses of PFS

Characteristic	Subgroup	PFS Events/No. of Patients (%)	Median PFS, Months (95% CI) [Interquartile Range]	1-Year PFS Rate, % (95% CI)	2-Year PFS Rate, % (95% CI)
All	–	558/1021 (54.7)	25.5 (23.7–27.6) [14.3–NE]	82.6 (80.0–84.8)	53.0 (49.7–56.1)
Ascites at baseline	Yes	140/191 (73.3)	16.5 (14.9–17.6)* [12.2–26.1]	75.1 (68.1–80.8)*	30.1 (23.5–36.9)*
	No	418/830 (50.4)	29.4 (26.6–31.3)* [16.3–NE]	84.3 (81.5–86.7)*	58.4 (54.8–61.8)*
MRC high risk	Yes	324/468 (69.2)	18.3 (16.8–20.6) [12.3–33.0]	76.5 (72.3–80.2)	37.1 (32.6–41.7)
	No	234/553 (42.3)	32.0 (30.9–40.2)* [19.4–NE]	87.8 (84.6–90.3)*	66.5 (62.2–70.5)*
Stage	IIIB–IV	495/785 (63.1)	21.6 (20.6–23.0) [12.8–39.6]	79.9 (76.8–82.6)	45.5 (41.8–49.0)
Paclitaxel schedule	Weekly	42/71 (59.2)	27.9 (18.3–35.4)* [14.7–NE]	83.7 (72.5–90.6)*	56.8 (44.1–67.6)*
	Every 3 weeks	516/950 (54.3)	25.2 (23.5–27.4)* [14.3–NE]	82.5 (79.8–84.8)*	52.7 (49.3–56.0)*
Bevacizumab dose	7.5 mg/kg	45/106 (42.5)	NE (23.5–NE)*	83.4 (74.7–89.4)	58.5 (48.1–67.5)
	15 mg/kg	513/909 (56.4)	25.1 (22.8–27.2)*	82.5 (79.7–84.9)	52.4 (48.9–55.7)

*Post hoc exploratory analyses. All other subgroup analyses were prespecified in the statistical analysis plan. MRC, Medical Research Council; NE, not estimable.

GOG-0218. Focusing on the increased incidence of proteinuria compared with the randomized phase 3 trials, the most likely explanation seems to be the longer duration of bevacizumab exposure. Hypertension also seemed to be more common in ROSiA than in ICON7 or GOG-0218. Although hypertension onset was typically within the first months of bevacizumab therapy, the duration of bevacizumab may nevertheless have been a contributing factor. Grade 3 or higher-grade hypertension first occurred after 1 year in 20% of those with this AE, either as a new event or worsening of previous lower-grade hypertension. Another important consideration is that 33% of patients had ongoing hypertension at baseline. In addition, AEs were graded according to National Cancer Institute’s Common Terminology Criteria for Adverse Events version 3.0 in ICON7 and GOG-0218, but by version 4.03 in ROSiA. Hypertension grading differs considerably between the 2 versions, with lower thresholds in the later version. Clinical safety data across tumor types suggest that bevacizumab-associated hypertension is dose dependent⁹; thus, administration of 15 mg/kg in most patients in ROSiA may partially explain the increased incidence compared with ICON7 (although not compared with GOG-0218) (Appendix Table A4, <http://links.lww.com/IGC/A417>). Our results cannot address the question of the optimal dose of bevacizumab, as only 10% of patients received bevacizumab at 7.5 mg/kg. Importantly, the proportions of patients discontinuing bevacizumab because of proteinuria or hypertension were relatively low (5% and 3%, respectively).

Apart from proteinuria and hypertension, there was little evidence that prolonging bevacizumab exposure increased bevacizumab toxicity. The relatively low incidence of gastrointestinal perforation, thromboembolic events, and other AEs of special interest with longer bevacizumab exposure provides reassurance that extending maintenance bevacizumab therapy does not have a detrimental effect on tolerability.

Efficacy was a secondary end point of the ROSiA study. Accepting that this is a single-arm study, the efficacy results raise some intriguing hypotheses. Median PFS

in ROSiA is the longest reported to date for frontline bevacizumab-containing therapy, both overall (25.5 months) and in the subgroup defined as “high risk” in Medical Research Council analyses (18.3 months). In the non–high-risk subgroup, median PFS was 32.0 months in the ROSiA study. As there was extensive censoring from 24 months onward, this median value with events in only 42% of patients is immature and yet is markedly longer than the median PFS of 25.0 months in the non–high-risk subgroup of ICON7¹⁰ and substantially longer than the 12-month maximum duration of bevacizumab treatment in the ICON7 trial. This observation raises the interesting hypothesis that the longer duration of bevacizumab in ROSiA, often until disease progression, contributes to an apparently extended PFS compared with that observed in this population within ICON7.

The less frequent tumor assessments in ROSiA may lead to an overestimation of PFS. Nevertheless, these results provide a possible signal about the feasibility and potential benefit of extending bevacizumab exposure. To address this question more rigorously, the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group is currently conducting a prospective randomized phase 3 trial (AGO-OVAR17/BOOST; ClinicalTrials.gov NCT01462890) comparing 15 versus 30 months of bevacizumab therapy in combination with carboplatin and paclitaxel given for 6 cycles.

Overall survival results are immature with events in only 23% of patients. Unfortunately, further long-term follow-up is not planned within the framework of the study, as the ROSiA safety study was designed with PFS as the primary efficacy outcome rather than OS.

In summary, results from this large multinational frontline study in ovarian cancer indicate that extended bevacizumab-containing therapy is both tolerable and feasible. The single-arm study design does not allow us to draw definitive conclusions on the impact of treatment duration on efficacy; however, the median PFS of 25.5 months is the longest reported to date.

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