Editorial Commentary

Progression after discontinuation of bevacizumab in the first-line treatment of ovarian cancer

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The ICON7 (1) and GOG-0218 (2) trials demonstrated that bevacizumab prolonged progression-free survival (PFS) in the first-line treatment of advanced ovarian cancer. In those trials, the difference in PFS between the control and bevacizumab throughout group was greatest when bevacizumab was administered at its maximum dose, and almost disappeared at 24 months. Thus, it was thought that progression due to early termination of bevacizumab may have reduced the efficacy of bevacizumab.

The AGO-OVAR 17 Bevacizumab Ovarian Optimal Standard Treatment (BOOST) trial (3) was an open-label, randomized, phase III trial testing the superiority of prolonged bevacizumab administration in the first-line treatment of advanced ovarian cancer, and the primary endpoint was PFS. In this trial, patients with stage IIB-IV ovarian cancer received primary debulking surgery (PDS) followed by 6 cycles of chemotherapy (paclitaxel 175 mg/m^2 + carboplatin area under curve 5) plus bevacizumab (15 mg/kg every 3 weeks) for 15 months [bevacizumab (BEV)15 group] or 30 months (BEV30 group) beginning with the first or second cycle. The results showed no difference in PFS between treatment groups [hazard ratio 0.99; 95% confidence interval (CI): 0.85–1.15] and no difference in overall survival (OS) (hazard ratio 1.04; 95% CI: 0.87–1.23). It was then concluded that 15 months of bevacizumab treatment remains the standard of care.

In the BOOST trial, the Kaplan-Meier curve for PFS showed that during the period when bevacizumab was discontinued in the BEV15 group and bevacizumab was administered in the BEV30 group, PFS was higher in the BEV30 group than in the BEV15 group, with the difference appearing to be greatest at the 30-month point. Then the BEV30 group experienced more progressions in the period after bevacizumab was discontinued, resulting in a crossing of the survival curves of the two groups (*Figure 1*). This suggests that bevacizumab suppresses progression while it is being administered, but that progression rather increases after discontinuation. We examined the risk of progression during bevacizumab administration and after bevacizumab was discontinued based on the Kaplan-Meier curves presented in the papers for the ICON7 (1), GOG-0218 (2), and BOOST (3) trials (*Table 1*). The results showed that bevacizumab suppressed progression in months 0–15 (risk ratio, 0.67 and 0.72, respectively) in both the ICON7 and GOG-0218 trials, but increased progression in months 15–30 after bevacizumab was discontinued (risk ratio, 1.80 and 1.78, respectively). In the BOOST trial, the risk ratio of progression was the same in months 0–15 while bevacizumab was administered in both groups (risk ratio, 1.00), but the risk of progression in the BEV30

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group was lower in months 15–30 after bevacizumab was discontinued in the BEV15 group (risk ratio, 0.68), while there was an increase in progression in the BEV30 group in months 30–45 (risk ratio, 2.75). Thus, the results in the BOOST trial replicate the ICON7 and GOG-0218 trial data in terms of reduced progression during bevacizumab administration and increased progression after bevacizumab discontinuation.

The main mechanism of action of bevacizumab, an anti-VEGF-A antibody, is inhibition of angiogenesis in tumor tissue. It causes hypoxia and hyponutrition of tumor cells, which to some extent can cause tumor cell apoptosis and necrosis, but does not eradicate tumor cells. And even during bevacizumab treatment, hypoxia-induced VEGF-independent and perhaps somewhat slower angiogenesis can cause tumor growth, leading to relapse during bevacizumab treatment (4). On the other hand, if the tumor growth depends on the direct action of VEGF on tumor cells or on VEGF-dependent vascularization (4), tumor enlargement is suppressed during bevacizumab administration and relapse occurs after bevacizumab is discontinued. Normalization of blood vessels by anti-VEGF antibodies was previously shown to potentially increase intratumor concentrations of cytotoxic agents (5), but a more recent study reported that it rather decreases them (6). It should be noted that in the GOG-0218 study, bevacizumab did not increase the response rate to chemotherapy (7,8). In addition, tumor immunosuppression by VEGF (9) led to the expectation that bevacizumab would activate tumor immunity, but hypoxia caused by anti-VEGF antibodies can rather cause tumor immunosuppression (10). And in the IMagyn050 trial, atetzolizumab in the presence of bevacizumab did not prolong PFS in advanced ovarian cancer (11). Based on the current evidence, bevacizumab should be considered a cytostatic growth suppressor, not an eradicator of tumor cells (8).

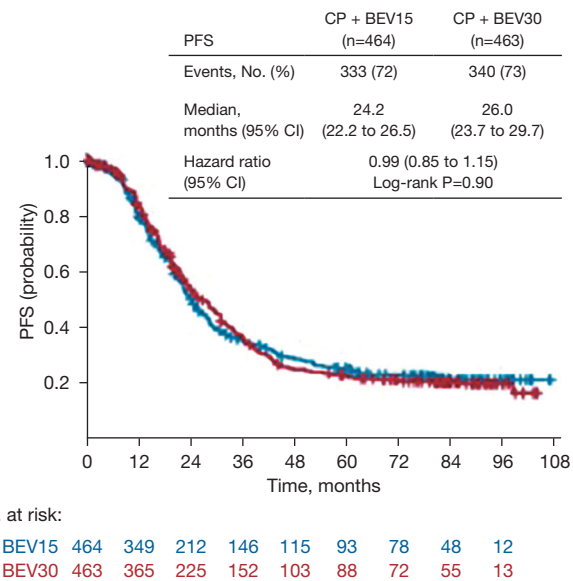

Figure 1 Kaplan-Meier curves for PFS in the BOOST trial. The BEV30 group had greater PFS than the BEV15 group at 30 months, but then progression of the BEV30 group increased and the survival curves crossed. *Fig. 2A* in reference (3) is shown with permission to reproduce. PFS, progression-free survival; CP, carboplatin plus paclitaxel; BEV, bevacizumab.

In the BOOST trial, 58% of patients underwent complete surgery with PDS, and the median PFS exceeded 24 months (3). Given the increased risk of progression after 30 months in the BEV30 group, a cohort with a shorter median PFS/OS might have had a statistically significant difference in survival time between the two groups. This is similar to the results of the ICON7 and GOG-0218 trials, which showed an increased benefit in the high-risk cases (1,2).

Table 1 Risk ratio of progression of the experimental arm (right) to the standard arm (left)

Time, months	ICON7 (1), *Fig. 3A*			GOG-0218 (2), *Fig. 2B*			BOOST (3), *Fig. 2A*		
	PFS		Risk ratio	PFS		Risk ratio	PFS		Risk ratio
	Control	Bevacizumab		Control	Bevacizumab		BEV15	BEV30	
0	1.00	1.00	–	1.00	1.00	–	1.00	1.00	–
15	0.55	0.70	0.67	0.33	0.52	0.72	0.66	0.66	1.00
30	0.35	0.34	1.8	0.15	0.20	1.78	0.38	0.47	0.68
45	–	–	–	–	–	–	0.30	0.25	2.75

PFS, progression-free survival; BEV, bevacizumab.

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Footnote

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