

14.6 Persistent, Recurrent, or Metastatic Cervical Cancer

Study GOG-0240

The safety and efficacy of bevacizumab were evaluated in patients with persistent, recurrent, or metastatic cervical cancer in a randomized, four-arm, multicenter study comparing bevacizumab with chemotherapy versus chemotherapy alone [GOG-0240 (NCT00803062)]. A total of 452 patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without bevacizumab, or paclitaxel and topotecan with or without bevacizumab.

The dosing regimens for bevacizumab, paclitaxel, cisplatin and topotecan were as follows:

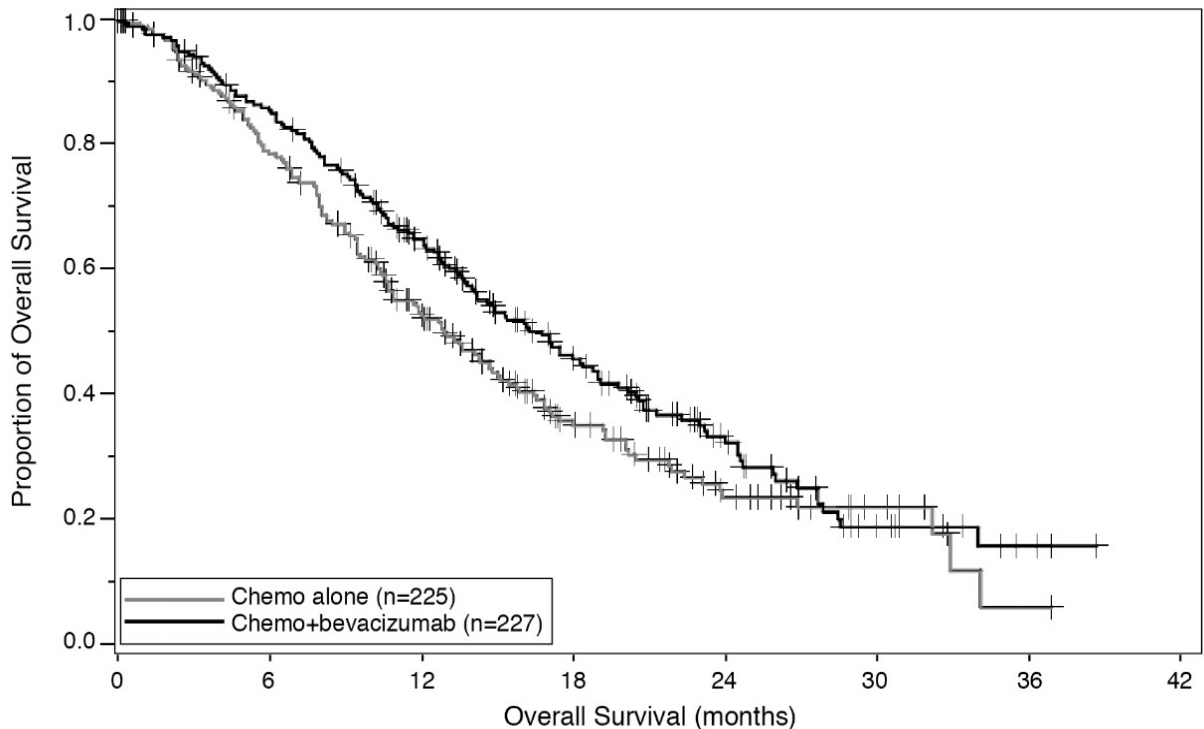
- Day 1: Paclitaxel 135 mg/m² over 24 hours, Day 2: cisplatin 50 mg/m² with bevacizumab;
- Day 1: Paclitaxel 175 mg/m² over 3 hours, Day 2: cisplatin 50 mg/m² with bevacizumab;
- Day 1: Paclitaxel 175 mg/m² over 3 hours with cisplatin 50 mg/m² with bevacizumab;
- Day 1: Paclitaxel 175 mg/m² over 3 hours with bevacizumab, Days 1-3: topotecan IV 0.75 mg/m² over 30 minutes

Patients were treated until disease progression or unacceptable adverse reactions. The main outcome measure was OS. Secondary outcome measures included ORR.

The median age was 48 years (20 to 85 years). Of the 452 patients randomized at baseline, 78% of patients were White, 80% had received prior radiation, 74% had received prior chemotherapy concurrent with radiation, and 32% had a platinum-free interval (PFI) of less than 6 months. Patients had a GOG performance status of 0 (58%) or 1 (42%). Demographic and disease characteristics were balanced across arms.

Results are presented in Figure 5 and Table 11.

Figure 5: Kaplan-Meier Curves for Overall Survival in Persistent, Recurrent, or Metastatic Cervical Cancer in Study GOG-0240



Number at Risk:

Chemo alone	225	171	102	49	21	8	1	0
Chemo+bevacizumab	227	188	128	73	35	12	3	0

Table 11: Efficacy Results in Study GOG-0240

Efficacy Parameter	Bevacizumab with Chemotherapy (N=227)	Chemotherapy (N=225)
Overall Survival		
Median, in months ^a	16.8	12.9
Hazard ratio (95% CI)	0.74 (0.58, 0.94)	
p-value ^b	0.0132	

^a Kaplan-Meier estimates.

^b log-rank test (stratified).

The ORR was higher in patients who received bevacizumab with chemotherapy [45% (95% CI: 39, 52)] compared to patients who received chemotherapy alone [34% (95% CI: 28,40)].

Table 12: Efficacy Results in Study GOG-0240

Efficacy Parameter	Topotecan and Paclitaxel with or without Bevacizumab (N=223)	Cisplatin and Paclitaxel with or without Bevacizumab (N=229)
Overall Survival		
Median, in months ^a	13.3	15.5
Hazard ratio (95% CI)	1.15 (0.91, 1.46)	
p-value	0.23	

^a Kaplan-Meier estimates.

The HR for OS with bevacizumab with cisplatin and paclitaxel as compared to cisplatin and paclitaxel alone was 0.72 (95% CI: 0.51, 1.02). The HR for OS with bevacizumab with topotecan and paclitaxel as compared to topotecan and paclitaxel alone was 0.76 (95% CI: 0.55, 1.06).

14.7 Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection

Study GOG-0218

The safety and efficacy of bevacizumab were evaluated in a multicenter, randomized, double-blind, placebo controlled, three arm study [Study GOG-0218 (NCT00262847)] evaluating the effect of adding bevacizumab to carboplatin and paclitaxel for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer (N=1873) following initial surgical resection. Patients were randomized (1:1:1) to one of the following arms:

- CPP: carboplatin (AUC 6) and paclitaxel (175 mg/m²) for six cycles, with concurrent placebo started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15: carboplatin (AUC 6) and paclitaxel (175 mg/m²) for six cycles, with concurrent bevacizumab started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15+: carboplatin (AUC 6) and paclitaxel (175 mg/m²) for six cycles, with concurrent bevacizumab started at cycle 2, followed by bevacizumab as a single agent every three weeks for a total of up to 22 cycles of therapy (n=623).

The main outcome measure was investigator-assessed PFS. OS was a secondary outcome measure.

The median age was 60 years (range 22-89 years) and 28% of patients were >65 years of age. Overall, approximately 50% of patients had a GOG PS of 0 at baseline, and 43% a GOG PS score of 1. Patients had either epithelial ovarian cancer (83%), primary peritoneal cancer (15%), or fallopian tube cancer (2%). Serous adenocarcinoma was the most common histologic type (85% in CPP and CPB15 arms, 86% in CPB15+ arm). Overall, approximately 34% of patients had resected FIGO Stage III with residual disease < 1 cm, 40% had resected Stage III with residual disease >1 cm, and 26% had resected Stage IV disease.

The majority of patients in all three treatment arms received subsequent antineoplastic treatment, 78.1% in the CPP arm, 78.6% in the CPB15 arm, and 73.2% in the CPB15+ arm. A higher proportion of patients in the CPP arm (25.3%) and CPB15 arm (26.6%) received at least one anti-angiogenic (including bevacizumab) treatment after discontinuing from study compared with the CPB15+ arm (15.6%).

Study results are presented in Table 13 and Figure 6.

Table 13: Efficacy Results in Study GOG-0218

Efficacy Parameter	Bevacizumab with carboplatin and paclitaxel followed by Bevacizumab alone (N=623)	Bevacizumab with carboplatin and paclitaxel (N=625)	Carboplatin and paclitaxel (N= 625)
Progression-Free Survival per Investigator			
Median, in months	18.2	12.8	12.0
Hazard ratio (95% CI) ^a	0.62 (0.52, 0.75)	0.83 (0.70, 0.98)	
p-value ^b	< 0.0001	NS	
Overall Survival^c			
Median, in months	43.8	38.8	40.6
Hazard ratio (95% CI) ^a	0.89 (0.76, 1.05)	1.06 (0.90, 1.24)	

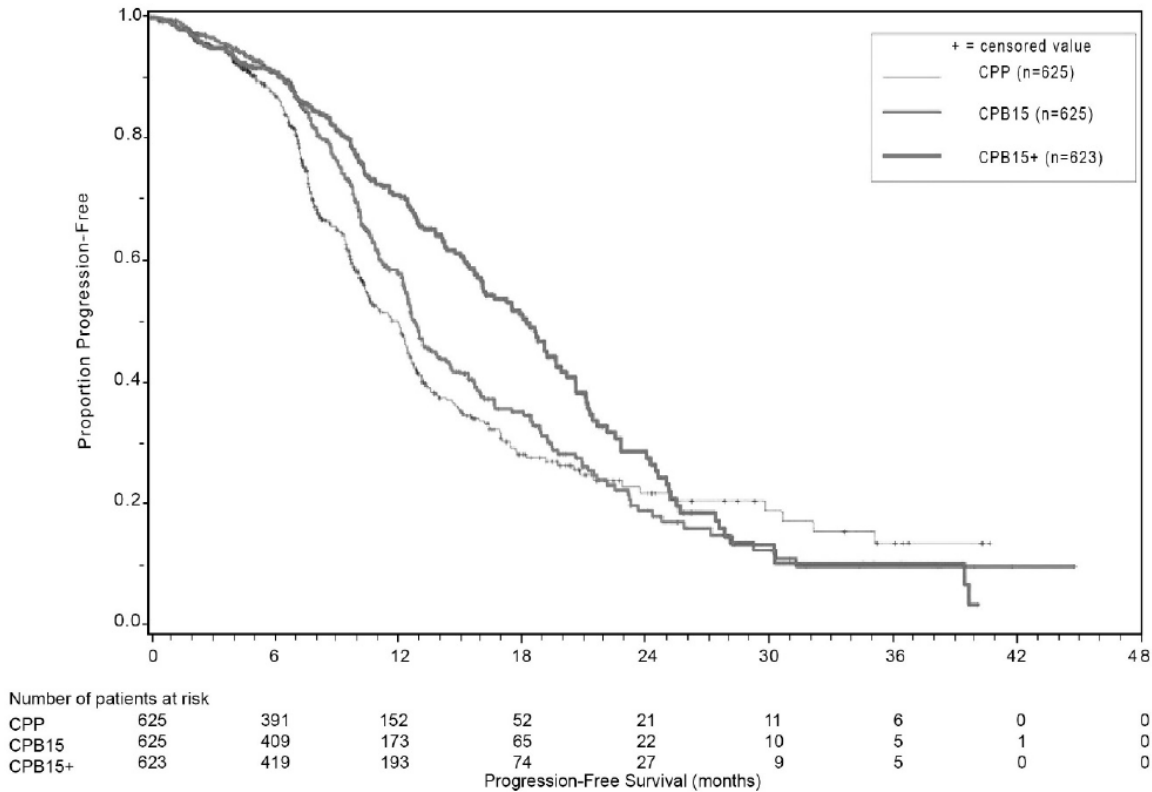
NS=not significant

^aRelative to the control arm; stratified hazard ratio

^bTwo-sided p-value based on re-randomization test

^cFinal overall survival analysis

Figure 6: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection in Study GOG-0218



14.8 Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study MO22224

The safety and efficacy of bevacizumab were evaluated in a multicenter, open-label, randomized study [MO22224 (NCT00976911)] comparing bevacizumab with chemotherapy versus chemotherapy alone in patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within <6 months from the most recent platinum-based therapy (N=361). Patients had received no more than 2 prior chemotherapy regimens. Patients received one of the following chemotherapy regimens at the discretion of the investigator: paclitaxel (80 mg/m² on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin 40 mg/m² on day 1 every 4 weeks; or topotecan 4 mg/m² on days 1, 8 and 15 every 4 weeks or 1.25 mg/m² on days 1-5 every 3 weeks). Patients were treated until disease progression, unacceptable toxicity, or withdrawal. Forty percent of patients on the chemotherapy alone arm received bevacizumab alone upon progression. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 61 years (25 to 84 years) and 37% of patients were ≥65 years. Seventy-nine percent had measurable disease at baseline, 87% had baseline CA-125 levels ≥2 times ULN and 31% had ascites at baseline. Seventy-three percent had a PFI of 3 months to 6 months and 27% had PFI of <3 months. ECOG performance status was 0 for 59%, 1 for 34% and 2 for 7% of the patients.

The addition of bevacizumab to chemotherapy demonstrated a statistically significant improvement in investigator-assessed PFS, which was supported by a retrospective independent review analysis. Results for the ITT population are presented in Table 14 and Figure 7. Results for the separate chemotherapy cohorts are presented in Table 15.

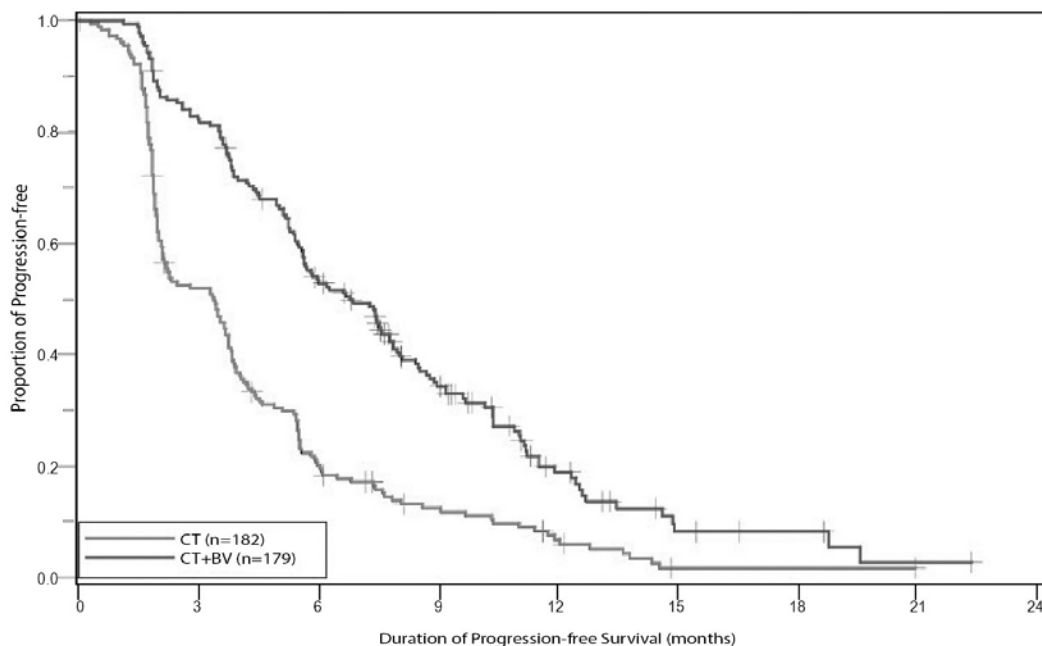
Table 14: Efficacy Results in Study MO22224

Efficacy Parameter	Bevacizumab with Chemotherapy (N=179)	Chemotherapy (N=182)
Progression-Free Survival per Investigator		
Median (95% CI), in months	6.8 (5.6, 7.8)	3.4 (2.1, 3.8)
HR (95% CI) ^a	0.38 (0.30, 0.49)	
p-value ^b	<0.0001	
Overall Survival		
Median (95% CI), in months	16.6 (13.7, 19.0)	13.3 (11.9, 16.4)
HR (95% CI) ^a	0.89 (0.69, 1.14)	
Overall Response Rate		
Number of Patients with Measurable Disease at Baseline	142	144
Rate, % (95% CI)	28% (21%, 36%)	13% (7%, 18%)
Duration of Response		
Median, in months	9.4	5.4

^a per stratified Cox proportional hazards model

^b per stratified log-rank test

Figure 7: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study MO22224



Number at Risk:	0	3	6	9	12	15	18	21	24
CT	182	92	35	18	9	1	1	0	0
CT+BV	179	144	91	51	19	6	4	1	0

