INTERVIEW

Robert A Burger, MD

Dr Burger is Professor in the Department of Surgical Oncology, Director of the Women's Cancer Center, Associate Director for Research in the Section of Gynecologic Oncology and Co-Director of the Ovarian Cancer Research Program at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

Tracks 1-12

Select Excerpts from the Interview

Track 1

DR LOVE: Would you describe the GOG-0218 trial and the rationale behind investigating bevacizumab in ovarian cancer?

DR BURGER: Ovarian cancer tends to overexpress VEGF, which is a central promoter of tumor angiogenesis. Bevacizumab, a VEGF-neutralizing monoclonal antibody, has demonstrated remarkable single-agent activity in recurrent ovarian cancer in at least two Phase II trials (Cannistra 2007; Burger 2007) and has been approved for patients with metastatic colorectal or non-small cell lung cancer.

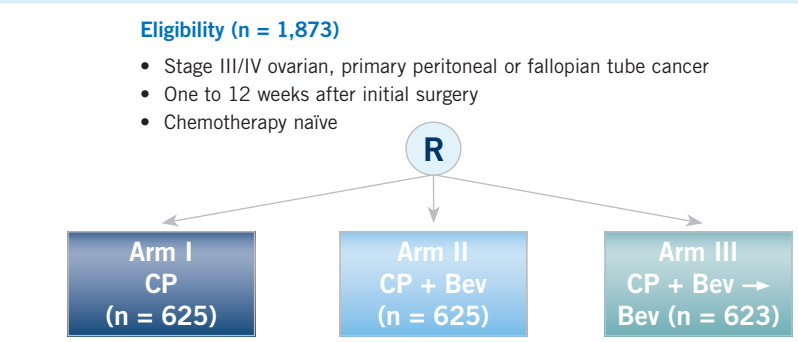
GOG-0218 was a randomized, placebo-controlled trial designed to investigate bevacizumab both concurrent with initial chemotherapy and as maintenance therapy (Burger 2010; [3.1]) for patients with Stage III/IV ovarian, primary peritoneal or fallopian tube cancer. The primary endpoint was PFS, with overall survival being one of the secondary endpoints.

DR LOVE: How was disease progression defined?

DR BURGER: The definition was based on two independent factors. One was serum CA125 progression using the Gynecologic Cancer Intergroup definition, which is fairly stringent, and the other was RECIST using standard imaging of the chest, abdomen and pelvis.

3.1

GOG-0218: A Phase III Trial of Chemotherapy versus Chemotherapy/ Bevacizumab (Bev) with or without Maintenance Bev



CP = carboplatin AUC 6, paclitaxel 175 mg/m^2; six three-week cycles
CP + Bev = CP + Bev 15 mg/kg with each cycle of CP
CP + Bev → Bev = CP + Bev followed by 16 three-week cycles of Bev 15 mg/kg

Burger RA et al. *Proc ASCO* 2010;**Abstract LBA1**.

Tracks 4-5

DR LOVE: Would you describe the safety and efficacy data?

DR BURGER: The adverse events data are largely similar to those from prior studies in metastatic nongynecologic cancer (Burger 2010; [3.2]). The incidence of gastrointestinal perforations, a safety signal in previous studies in ovarian cancer, was less than three percent on all three arms. The incidence of thromboembolic events was similar across the arms.

In terms of efficacy, the trial showed an improved PFS for patients receiving concurrent bevacizumab followed by maintenance bevacizumab (Burger 2010; [3.3]).

The interpretation of the survival data is limited at this time because only 24 percent of patients across the study have died of the disease. Somewhat fewer

deaths occurred on arm three versus the other arms, but the median overall survival rates are not currently statistically different.

In addition, because unblinding of the treatment arm may occur at the time of disease progression, a high potential for crossover to bevacizumab in subsequent lines of therapy may neutralize any effect we see on overall survival.

3.2

GOG-0218: Select Adverse Events

Adverse event	Arm I CP (n = 601)	Arm II CP + Bev (n = 607)	Arm III CP + Bev → Bev (n = 608)
GI events (Grade ≥II)*	1.2%	2.8%	2.6%
HTN (Grade ≥II)	7.2%	16.5%	22.9%
Proteinuria (Grade ≥III)	0.7%	0.7%	1.6%
Venous thromboembolism	5.8%	5.3%	6.7%
Arterial thromboembolism	0.8%	0.7%	0.7%
CNS bleeding	0%	0%	0.3%
Non-CNS bleeding (Grade ≥III)	0.8%	1.3%	2.1%

* GI events include perforation, fistula, necrosis and leak.
CP = carboplatin/paclitaxel; Bev = bevacizumab

Burger RA et al. *Proc ASCO* 2010;**Abstract LBA1**.

Track 6

DR LOVE: What is your take on the major efficacy findings in the GOG-0218 trial?

DR BURGER: I believe one always needs to examine the methods used to assess the disease and the risk level in the population studied. In the GOG-0218 trial, the median PFS in the control arm was 10 months, which was much lower than the PFS of 14 months expected on the basis of the historical information from recent Phase III trials enrolling patients with similar eligibility criteria.

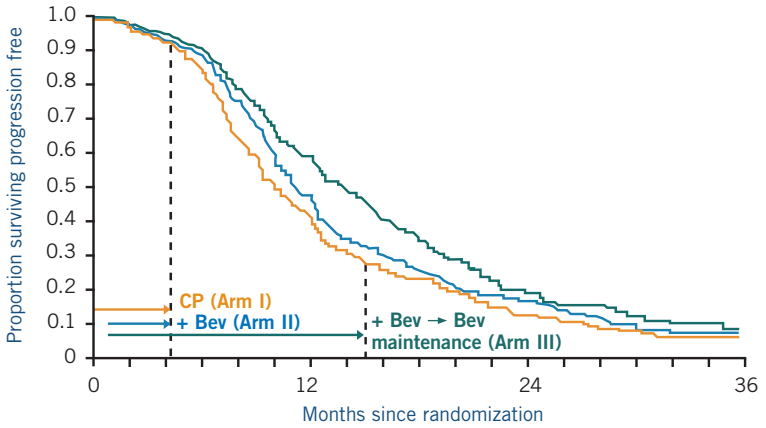
Two thirds of the patients in GOG-0218 had either Stage IV disease or suboptimally debulked Stage III disease, which essentially elevates the risk of progression. Despite that, the hazard ratio in GOG-0218 was 0.717. In Phase III trials that were positive for overall survival, the hazard ratio for PFS was in a similar range.

In the GOG-172 trial (Armstrong 2006), which showed a 16-month improvement in overall survival in favor of intraperitoneal chemotherapy, the hazard ratio for PFS was 0.8. Similarly, GOG-111 (McGuire 1996), establishing paclitaxel as part of standard therapy, demonstrated improvement in PFS, similar to what we saw in this trial.

Right now, I believe it is important to discuss the results of the GOG-0218 trial with patients, explain the impact and offer this approach as an option for treatment within standard care. ■

3.3

GOG-0218: Primary Endpoint — Progression-Free Survival (PFS)



	Arm I CP (n = 625)	Arm II CP + Bev (n = 625)	Arm III CP + Bev → Bev (n = 623)
Patients with event (%)	67.7	66.9	57.8
Median PFS, months	10.3	11.2	14.1
Hazard ratio	—	0.908	0.717
One-sided *p*-value	—	0.080	<0.0001

CP = carboplatin/paclitaxel; Bev = bevacizumab

With permission from Burger RA et al. *Proc ASCO* 2010;**Abstract LBA1**.

SELECT PUBLICATIONS

Armstrong DK et al. **Intraperitoneal cisplatin and paclitaxel in ovarian cancer.** *N Engl J Med* 2006;354(1):34-43.

Burger RA et al. **Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study.** *Proc ASCO* 2010;**Abstract LBA1**.

Burger RA et al. **Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: A Gynecologic Oncology Group study.** *J Clin Oncol* 2007;25(33):5165-71.

Cannistra SA et al. **Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer.** *J Clin Oncol* 2007;25(33):5180-6.

McGuire WP et al. **Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer.** *N Engl J Med* 1996;334(1):1-6.

Naumann RW et al. **Practice patterns of intraperitoneal chemotherapy in women with ovarian cancer.** *Gynecol Oncol* 2009;114(1):37-41.