

Ovarian Cancer™

U P D A T E

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Thomas J Herzog, MD

Deborah K Armstrong, MD

Robert A Burger, MD

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Ovarian Cancer Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Optimal oncologic management of ovarian cancer begins with intensive surgical staging and cytoreduction, followed by postoperative chemotherapy and, in most cases, subsequent medical management when platinum-resistant relapsed disease prevails. Although many single-agent and combination cytotoxic recurrence regimens have been studied, only recently has the advent of antibody and small-molecule growth-inhibitory targeted agents been integrated into the ovarian cancer research milieu. It is hoped that the results from these trials will lead to the emergence of new therapeutic agents and changes or enhancements in the indications for existing treatment strategies, ultimately improving the duration and quality of life for patients with metastatic ovarian cancer. In order to offer optimal care to the population of patients with ovarian cancer — including the option of clinical trial participation — practicing oncologists must be well informed of these advances. By providing access to the latest research developments and expert perspectives through one-on-one discussion with leading investigators, *Ovarian Cancer Update* will assist medical and gynecologic oncologists with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Consider the utility of CA125 serum levels in monitoring disease progression and making treatment decisions.
- Compare and contrast the risks and benefits of intraperitoneal and intravenous chemotherapy regimens when devising management strategies for optimally debulked Stage II or Stage III ovarian cancer.
- Develop an evidence-based algorithm for the systemic treatment of recurrent platinum-sensitive and platinum-resistant ovarian cancer that optimizes long-term patient outcomes and quality of life.
- Describe emerging data on the activity of poly(ADP-ribose) polymerase (PARP) inhibitors in patients with BRCA-like advanced ovarian cancer.
- Summarize the existing data and ongoing clinical trials focused on angiogenesis inhibition in ovarian cancer, and identify patients who may benefit from this therapeutic approach.
- Recall the rationale and activity of novel targeted agents under investigation for the treatment of ovarian cancer.
- Counsel appropriately selected patients with ovarian cancer about the availability of and participation in ongoing clinical trials.

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INTERVIEW

Thomas J Herzog, MD

Dr Herzog is Director of Gynecologic Oncology and Physicians and Surgeons Alumni Professor of Clinical Gynecology and Obstetrics at Columbia University Medical Center in New York, New York.

Tracks 1-12

- Track 1 Case discussion:** A 44-year-old woman and physician with a large-volume, Grade III papillary serous adenocarcinoma undergoes optimal cytoreductive surgery and intraperitoneal (IP) chemotherapy
- Track 2** IP chemotherapy for patients with Stage III ovarian cancer (OC)
- Track 3** Supportive care for patients receiving IP chemotherapy
- Track 4** Critical appraisal of the survival benefit observed with IP chemotherapy
- Track 5** Perspectives on the GOG-0218 trial evaluating bevacizumab with chemotherapy
- Track 6** Single-agent bevacizumab for patients with recurrent OC
- Track 7 Case discussion:** A 58-year-old woman with a BRCA1 mutation and optimally cytoreduced Grade III OC completes carboplatin/paclitaxel and subsequently experiences a progressive increase in CA125 level
- Track 8** Treatment options for patients with platinum-resistant, recurrent OC
- Track 9** Clinical algorithm for patients with platinum-sensitive, recurrent OC
- Track 10** Tolerability of combination regimens — Gemcitabine/platinum and liposomal doxorubicin/platinum
- Track 11 Case discussion:** A 61-year-old woman with suboptimally cytoreduced OC and ascites receives carboplatin/paclitaxel and experiences an early, progressive increase in CA125 level
- Track 12** Use of endocrine therapy and tamoxifen for OC

Select Excerpts from the Interview

Tracks 2-3

► **DR LOVE:** What is your approach to intraperitoneal (IP) chemotherapy in ovarian cancer?

► **DR HERZOG:** I believe it is crucial for patients to complete therapy without significantly deviating from the schedule and doses that were administered in the GOG-0172 trial, which reported a large overall survival difference (Armstrong 2006; [1.1]).

The only initial change I make is to shorten the 24-hour paclitaxel infusion on day one to a three-hour infusion for convenience. After the first or second

cycle, I consider how the patients are faring. Only if they are not tolerating therapy am I willing to lower the dose.

Choosing the correct patient for IP therapy is key. IP therapy should be avoided for patients with significant comorbidities, elderly patients and those with impaired performance statuses.

► **DR LOVE:** What supportive care is necessary when administering IP chemotherapy?

► **DR HERZOG:** I consider hydration to be vital. I have had one patient and have seen reports of others who sustained severe renal damage when not adequately hydrated, so this is an extremely important issue.

It is also important to understand that these patients must know that if they go home and are not tolerating oral intake well, that is an emergency and they need to call their doctors immediately.

We also use growth factors liberally in terms of white blood cell support. The rate of febrile neutropenia warrants consideration of prophylactic growth factors for all of these patients.

1.1

GOG-0172: A Phase III Trial of Intraperitoneal versus Intravenous Chemotherapy for Stage III Ovarian Cancer

	Intravenous therapy group	Intraperitoneal therapy group	Relative risk	p-value
Progression-free survival	18.3 months	23.8 months	0.80	0.05
Overall survival	49.7 months	65.6 months	0.75	0.03

Armstrong DK et al. *N Engl J Med* 2006;354(1):34-43.

Track 5

► **DR LOVE:** What are your thoughts on the results presented at ASCO of the GOG-0218 trial evaluating bevacizumab with chemotherapy after debulking surgery?

► **DR HERZOG:** On the basis of the safety and efficacy data presented at the ASCO plenary session (Burger 2010; [3.2, 3.3]), it is reasonable to say that up-front concomitant bevacizumab/chemotherapy followed by maintenance bevacizumab is an option in the initial management of ovarian cancer.

The median progression-free survival (PFS) improved from 10.3 months to 14.1 months, and although I would have preferred a larger difference, this patient population had poorer prognoses overall and the hazard ratio looks good.

The survival data are not mature yet, and before bevacizumab is considered the standard approach for the initial management of ovarian cancer we need to see mature survival data from the GOG-0218 trial.

Tracks 8-10

▶ **DR LOVE:** How do you approach recurrent ovarian cancer?

▶ **DR HERZOG:** The approach to treatment of recurrent ovarian cancer is different depending on whether the disease is considered to be platinum resistant or platinum sensitive.

The difference between these two groups is defined by the treatment-free interval after initial platinum-containing chemotherapy. Disease that recurs within six months of initial platinum-containing therapy is deemed platinum resistant, and that which recurs after six months of such therapy is considered platinum sensitive.

Platinum-resistant ovarian cancer is usually treated with single-agent chemotherapy. Liposomal doxorubicin is the most common drug in my practice in this setting because of the convenient schedule and reasonable toxicity profile. Other options include topotecan, which can be administered on either the FDA-approved schedule of daily times five or the weekly schedule. Additional single-agent options to consider in this setting are docetaxel, etoposide, gemcitabine and bevacizumab.

Among patients with platinum-sensitive, symptomatic disease or those who have experienced recurrence beyond one year of initial therapy, I consider platinum/paclitaxel or platinum/gemcitabine. Another regimen combining a platinum agent and pegylated liposomal doxorubicin has demonstrated improved PFS in comparison to carboplatin/paclitaxel in this setting (Pujade-Lauraine 2009; [1.2]).

The toxicity profiles were different, with patients in the pegylated liposomal doxorubicin group experiencing fewer hypersensitivity reactions. So this is a third option that should be considered when selecting a platinum-containing doublet for platinum-sensitive ovarian cancer.

Another option I consider for patients with platinum-sensitive disease and fewer than 18 months of initial treatment is using something other than a taxane, as they received six cycles of a taxane in the initial regimen.

We know that we can likely replace the nonplatinum agent in the doublet without compromising efficacy, and we have a different toxicity profile when using a nontaxane. Additional benefit may also be gained — perhaps a different mechanism of action with the hope of overcoming the initial resistance.

All of these factors compel me to use a platinum and gemcitabine most commonly and sometimes to consider a platinum and pegylated liposomal doxorubicin for patients with platinum-sensitive disease.

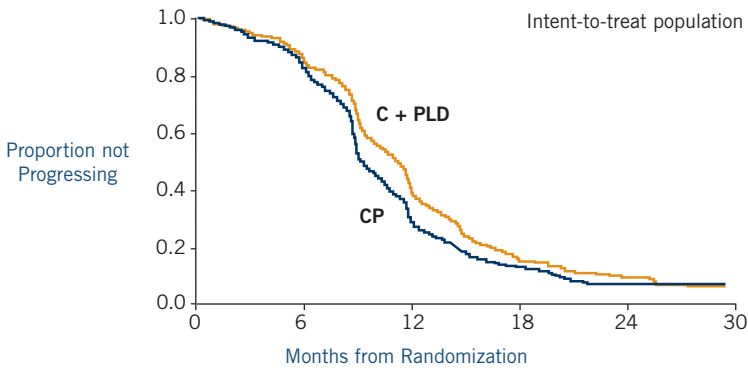
► **DR LOVE:** What is your experience with the side effects and tolerability of platinum/gemcitabine or platinum/liposomal doxorubicin in ovarian cancer?

► **DR HERZOG:** Platinum/gemcitabine is well tolerated overall. One issue is the day-eight dosing. Approximately half of patients require some dose reduction on day eight. When you reach the correct dose for the patient, it is tolerated well.

I have administered the platinum/liposomal doxorubicin combination to probably 10 or 15 patients. One needs to be mindful of myelosuppression. However, patients like the 28-day schedule, which was used in the CALYPSO trial. I have not seen much hand-foot syndrome with this regimen either. ■

1.2

CALYPSO: Progression-Free Survival (PFS) with Carboplatin (C) and Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin and Paclitaxel (P) in Relapsed Platinum-Sensitive Ovarian Cancer



In PLD/C arm, PLD dose was 30 mg/m²

	C + PLD	CP	p-value (superiority)	p-value (inferiority)
Median PFS, mo	11.3	9.4	0.005	<0.001

With permission from Pujade-Lauraine E et al. *Proc ASCO* 2009; **Abstract LBA5509**.

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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 in the primary treatment of advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer: A Gynecologic Oncology Group study.** *Proc ASCO* 2010; **Abstract LBA1**.

Kose MF et al. **A phase II study of gemcitabine plus carboplatin in platinum-sensitive, recurrent ovarian carcinoma.** *Gynecol Oncol* 2005;96(2):374-80.

Pujade-Lauraine E et al. **A randomized phase III study of carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in relapsed platinum-sensitive ovarian cancer (OC): CALYPSO study of the Gynecologic Cancer Intergroup (GCIG).** *Proc ASCO* 2009; **Abstract LBA5509**.



INTERVIEW

Deborah K Armstrong, MD

Dr Armstrong is Associate Professor of Oncology, Gynecology and Obstetrics at The Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University in Baltimore, Maryland.

Tracks 1-14

- Track 1** Efficacy and safety of chemotherapy/bevacizumab followed by maintenance bevacizumab in the GOG-0218 trial
- Track 2** Clinical implications of the GOG-0218 study
- Track 3** Olaparib for patients with advanced serous OC with known and unknown BRCA mutations
- Track 4** Emerging clinical issues with the use of PARP inhibitors
- Track 5** Efficacy and safety of farletuzumab with or without chemotherapy for relapsed OC
- Track 6** BIBF 1120, a novel, oral multitargeted tyrosine kinase inhibitor of VEGFR, PDGFR and FGFR
- Track 7** Investigations of the HER dimerization inhibitor pertuzumab in OC
- Track 8** **Case discussion:** A 73-year-old woman with a BRCA1 mutation and a 40-year history of repeated diagnosis of primary and recurrent breast and ovarian cancer
- Track 9** **Case discussion:** A 60-year-old woman with a large-volume, high-grade serous carcinoma with extensive pelvic and peritoneal implants and ascites does not experience a response to neoadjuvant paclitaxel/carboplatin or topotecan but experiences a 21-month response to bevacizumab on the GOG-170D trial
- Track 10** **Case discussion:** A 69-year-old woman on the Prostate, Lung, Colorectal and Ovarian Cancer screening study is diagnosed with Stage IIIC OC
- Track 11** A prospective screening study using the risk of ovarian cancer algorithm
- Track 12** GOG-0252: A Phase III clinical trial of bevacizumab with intravenous (IV) versus IP chemotherapy in Stage II to IV OC
- Track 13** Therapeutic options for recurrent, platinum-resistant OC
- Track 14** Single-agent and combination platinum-containing chemotherapy for recurrent, platinum-sensitive OC

Select Excerpts from the Interview

Track 5

► **DR LOVE:** What is the mechanism of action of the novel agent farletuzumab in ovarian cancer?

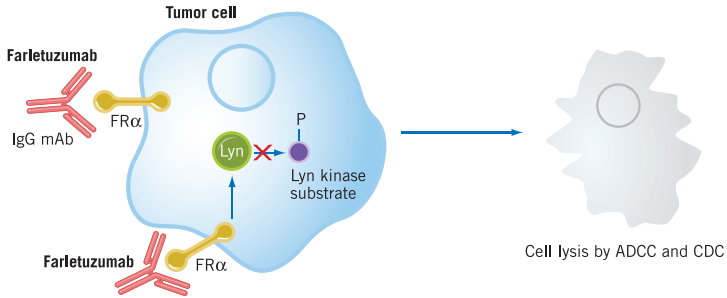
► **DR ARMSTRONG:** Farletuzumab is an interesting targeted agent. Folate is taken up into cells by two mechanisms: one is the folate receptor alpha and

the other is reduced folate carrier. The folate receptor alpha is highly overexpressed in ovarian cancer, on the order of 90-plus percent, but is largely absent from normal tissues.

Farletuzumab is an antibody that targets folate receptor alpha (2.1), and because of the differential expression of folate receptor alpha on ovarian cancer cells and normal tissues, folate can still penetrate normal cells naturally through the reduced folate carrier.

2.1

Farletuzumab: Bimodal Mechanism of Action



Farletuzumab, a humanized monoclonal antibody (mAb), demonstrates a high affinity to the folate receptor alpha (FR α). Binding of mAb to FR α results in a bimodal mechanism of action to suppress tumor growth: (1) promotion of cell lysis by antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) and (2) decreased cellular proliferation through the inhibition of Lyn kinase substrate phosphorylation (P).

Adapted from White AJ et al. *Proc ASCO* 2010; **Abstract 5001**.

2.2

Phase II Trial: Activity of Farletuzumab and Carboplatin/Paclitaxel in Platinum-Sensitive Relapsed Ovarian Cancer (n = 44)

CA125 normalization	RECIST response (CR + PR)	RECIST patient benefit (CR + PR + SD)	Median progression-free interval by CA125 criterion
89%	70%	93%	10 months

The response rate among patients with a first progression-free interval of less than 12 months was unexpectedly high, comparable to that for patients with a first progression-free interval of more than 12 months.

Preliminary data for this study also indicated that farletuzumab with carboplatin/paclitaxel significantly increases the objective response rate compared to the objective response rates in historic data with carboplatin/paclitaxel in platinum-sensitive first-relapse ovarian cancer and increases the duration of second remission compared to first remission.

CR = complete response; PR = partial response; SD = stable disease

White AJ et al. *Proc ASCO* 2010; **Abstract 5001**.

A Phase II trial investigating farletuzumab enrolled patients with low-volume or asymptomatic disease to receive single-agent farletuzumab alone, and those with high-volume or symptomatic disease went on to receive chemotherapy combined with farletuzumab. The overall CA125 response and RECIST response to the combination are quite high (White 2010; [2.2]).

In addition, in 21 percent of the patients receiving farletuzumab/chemotherapy, the second progression-free interval was longer than their initial progression-free interval with chemotherapy alone. These data have led to ongoing trials in platinum-resistant disease, in addition to the registrational study in platinum-sensitive disease with paclitaxel and carboplatin.

Track 6

► **DR LOVE:** What are your thoughts on anti-angiogenic tyrosine kinase inhibitors being evaluated in ovarian cancer?

► **DR ARMSTRONG:** Many oral angiogenesis inhibitors are currently in development for ovarian cancer.

BIBF 1120 is one of these VEGF tyrosine kinase inhibitors, and it is being investigated in combination with chemotherapy in a large, placebo-controlled, randomized Phase III study in the front-line management of ovarian cancer (2.3). Another oral agent currently being investigated in a Phase II setting is sorafenib in combination with bevacizumab.

2.3

Randomized Placebo-Controlled Phase III Trial of BIBF 1120 in Combination with Carboplatin/Paclitaxel as First-Line Treatment for Ovarian Cancer



Primary endpoint is progression-free survival.

www.clinicaltrials.gov. Identifier NCT01015118.

Track 12

► **DR LOVE:** What new research strategies are being used with IP chemotherapy in ovarian cancer?

► **DR ARMSTRONG:** Many clinical trials are investigating carboplatin instead of cisplatin when administering IP chemotherapy. A trial investigating IP carboplatin, IP paclitaxel and IV bevacizumab has been published and demonstrated that the addition of bevacizumab is feasible (Krasner 2010; [2.4]).

In addition, the Gynecologic Oncology Group is investigating the addition of bevacizumab to both IV and IP chemotherapy in a Phase III clinical trial in ovarian cancer (2.5). This trial, GOG-0252, also has a maintenance bevacizumab component that continues until disease progression. ■

2.4

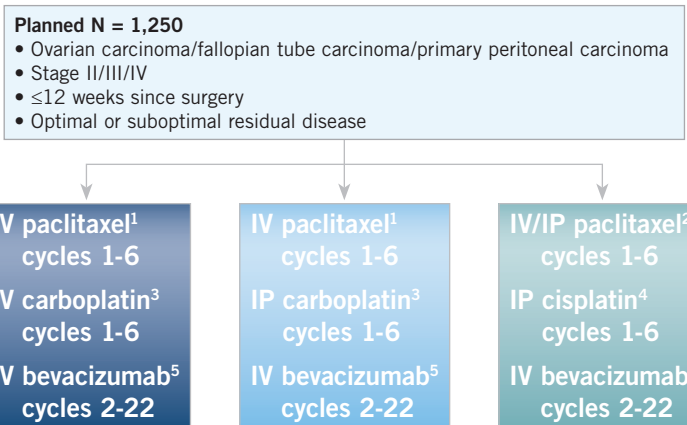
Tolerability of Intraperitoneal Carboplatin and Paclitaxel with Intravenous Bevacizumab (n = 40)

Febrile neutropenia	Grade III-IV neutropenia	Grade III-IV thrombocytopenia	Grade III-IV hypertension	Bowel perforation	Pulmonary emboli
0%	25%	12.5%	0%	0%	5%

Krasner CN et al. *Proc ASCO* 2010; **Abstract 5037**.

2.5

A Phase III Study of Bevacizumab with IV versus IP Chemotherapy in Ovarian, Fallopian Tube and Primary Peritoneal Carcinoma



Primary endpoint is progression-free survival.
Each cycle is 21 days in duration.

¹ Paclitaxel is administered on days 1, 8 and 15; ² Paclitaxel is administered IV on day 1 and IP on day 8; ³ Carboplatin is administered on day 1 of cycles 1-6; ⁴ Cisplatin is administered on day 2 of cycles 1-6; ⁵ Bevacizumab is administered with chemotherapy on day 1 of cycles 2-6 and alone on day 1 of cycles 7-22.

www.clinicaltrials.gov. Identifier NCT00951496.

SELECT PUBLICATIONS

Krasner CN et al. **Tolerability and pharmacokinetics of intraperitoneal carboplatin and paclitaxel with intravenous bevacizumab.** *Proc ASCO* 2010; **Abstract 5037**.

White AJ et al. **Efficacy and safety of farletuzumab, a humanized monoclonal antibody to folate receptor alpha, in platinum-sensitive relapsed ovarian cancer subjects: Final data from a multicenter phase II study.** *Proc ASCO* 2010; **Abstract 5001**.



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

- Track 1** GOG-0218: A Phase III trial of chemotherapy versus chemotherapy/bevacizumab with or without maintenance bevacizumab in the primary treatment of advanced OC
- Track 2** Incidence of and risk factors for bevacizumab-associated bowel perforation in OC
- Track 3** Rates of arterial and venous events in the GOG-0218 study
- Track 4** Tolerability of bevacizumab in the GOG-0218 study
- Track 5** GOG-0218: Progression-free survival advantage with maintenance bevacizumab
- Track 6** Overall survival endpoint in clinical trials of first-line therapy for advanced OC
- Track 7** Application of the GOG-0218 trial to clinical practice
- Track 8** Potential benefits of extended duration of treatment with bevacizumab
- Track 9** Translational studies in GOG-0218
- Track 10** **Case discussion:** A 46-year-old woman with a BRCA1 mutation is diagnosed with Stage IIIC OC and undergoes radical resection, periaortic lymphadenectomy and partial sigmoid colectomy followed by IV carboplatin/paclitaxel
- Track 11** Bevacizumab in combination with chemotherapy for patients with Stage III OC who undergo bowel resection
- Track 12** Activity of single-agent PARP inhibitor therapy with olaparib in BRCA-mutated, advanced OC

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?

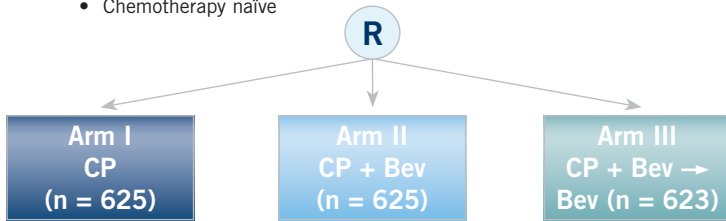
► **DR BURGER:** The definition was based on two independent factors. One was serum CA125 progression using the Gynecologic Cancer Intergroup definition, which is fairly stringent, and the other was RECIST using standard imaging of the chest, abdomen and pelvis.

3.1

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

Eligibility (n = 1,873)

- Stage III/IV ovarian, primary peritoneal or fallopian tube cancer
- One to 12 weeks after initial surgery
- Chemotherapy naïve



CP = carboplatin AUC 6, paclitaxel 175 mg/m²; 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.

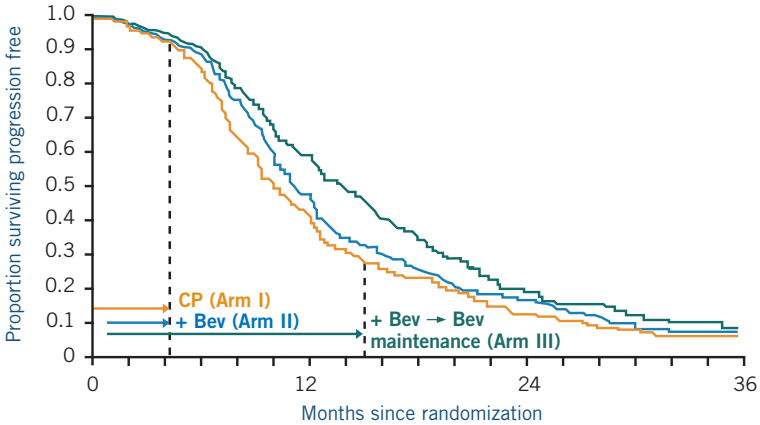
Two thirds of the patients in GOG-0218 had either Stage IV disease or suboptimally debulked Stage III disease, which essentially elevates the risk of progression. Despite that, the hazard ratio in GOG-0218 was 0.717. In Phase III trials that were positive for overall survival, the hazard ratio for PFS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

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INTERVIEW

Robert F Ozols, MD, PhD

Dr Ozols is Chief Clinical Officer, Emeritus at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

Tracks 1-13

- Track 1 Case discussion:** A 70-year-old woman with optimally debulked OC experiences disease relapse after receiving maintenance bevacizumab on the GOG-0218 study
- Track 2** Incorporation of up-front bevacizumab into the management of OC
- Track 3** Relevance of progression-free survival as an endpoint in OC
- Track 4** Evolving role of bevacizumab in the initial management of OC
- Track 5** Targeting PARP in patients with germline BRCA mutations
- Track 6** Concept of BRCAness in patients with the wild-type BRCA gene
- Track 7 Case discussion:** A 65-year-old woman with relapsed OC and known BRCA mutation receives single-agent olaparib in a Phase II study
- Track 8 Case discussion:** A 60-year-old woman with optimally debulked OC develops recurrent disease six months after IP cisplatin/paclitaxel and receives carboplatin/gemcitabine
- Track 9** Investigating IV bevacizumab with IP chemotherapy in optimally debulked OC
- Track 10** Targeting the folate receptor with the humanized monoclonal antibody farletuzumab in OC
- Track 11** Current status of pertuzumab in HER2-positive OC
- Track 12** Moving toward personalized treatment of relapsed platinum-sensitive OC
- Track 13** Weekly versus three-weekly paclitaxel in OC

Select Excerpts from the Interview

Tracks 1-4

► **DR LOVE:** What are your thoughts on the results of the GOG-0218 study (Burger 2010; [3.1, 3.2, 3.3])?

► **DR OZOLS:** I certainly would lean toward using chemotherapy/bevacizumab followed by maintenance bevacizumab, as I agree that a four-month improvement in PFS is a benefit. Some toxicity occurs and patients have to be aware of that, but overall I believe it is certainly a reasonable approach.

Because oncologists are familiar with using bevacizumab in other tumor types, they are not going to be afraid to administer it in this setting. Hypertension is manageable, and quality of life is good. Hopefully, we will obtain

more data from the GOG-0218 trial and additional ongoing studies. Some of these studies, such as ICON7, are also evaluating bevacizumab for earlier-stage ovarian cancer. If these additional studies are positive, they will add to the database indicating that we can incorporate bevacizumab into the front-line management of ovarian cancer.

 **Tracks 5-6**

▶ **DR LOVE:** Where are we currently in research on PARP inhibitors in ovarian cancer?

▶ **DR OZOLS:** The development of PARP inhibitors has been an exciting area in ovarian cancer. Approximately 10 percent of patients carry BRCA1 or BRCA2 mutations. Both of these are DNA repair genes and are needed by both normal tissue and tumor tissue.

Among patients with germline mutations of BRCA, tumor cells have little BRCA activity. One allele was lost with the germline mutation, and the remaining allele was lost when the cells became cancerous. So the tumor cells are dependent upon this alternate pathway known as PARP, which in normal tissue is relatively inconsequential because of the presence of a much more powerful BRCA DNA repair pathway. PARP inhibitors block this alternate pathway, which tumor cells are now dependent upon in the face of the BRCA mutation.

When PARP is inhibited, suddenly cancer cells have no ability to repair their DNA and undergo apoptosis. A Phase II study has shown dramatic responses with single-agent olaparib, a PARP inhibitor, in advanced chemotherapy-refractory ovarian cancer with BRCA mutation (Audeh 2010; [4.1]).

Theoretically, PARP inhibitors should work well as single agents and in combination with chemotherapy for patients with germline BRCA1 or BRCA2 mutations. Patients with serous ovarian tumors do not have germline mutations of BRCA1 or BRCA2. However, they may have relatively inactive BRCA pathways, which may have been blocked by mechanisms such as methylation. Essentially, these tumors may be functioning as if they do not have active BRCA pathways and thus may be sensitive to PARP inhibitors. So PARP inhibitors will be studied not only for patients with BRCA mutations but also for these patients with sporadic ovarian cancer and BRCAness.

4.1 Efficacy and Safety of Olaparib in Chemotherapy-Refractory Ovarian Cancer with BRCA1/BRCA2 Germline Mutation

RECIST response rate ¹	Clinical benefit rate ^{1,2}	Grade III/IV nausea ¹	Grade III/IV fatigue ¹
33%	52%	6%	3%

¹ Response rates, benefit rates and toxicities are with olaparib 400 mg PO BID (n = 33);
² Clinical benefit rate: RECIST response and/or confirmed ≥50 percent decline in CA125

Audeh MW et al. *Lancet* 2010;376(9737):245-51.

Track 11

► **DR LOVE:** What do we know about anti-HER2 therapy in ovarian cancer and pertuzumab specifically?

► **DR OZOLS:** Pertuzumab is a different type of monoclonal antibody and is a HER dimerization inhibitor. In a Phase I study pertuzumab demonstrated antitumor activity (Agus 2005). Data have also been reported with chemotherapy/pertuzumab (Makhija 2010), and efforts have been made to identify markers that could predict response to pertuzumab (Gordon 2006; Makhija 2010; [4.2]). ■

4.2

Progression-Free Survival with the Addition of Pertuzumab to Gemcitabine (Gem) in Platinum-Resistant Ovarian Cancer, Including Analysis by HER3 mRNA Expression

Progression-free survival	Gem/placebo	Gem/ pertuzumab	HR	<i>p</i> -value
All pts (n = 65, 65)	2.6 mo	2.9 mo	0.66	0.0708
Primary platinum resistant (n = 42, 48)	1.5 mo	2.9 mo	0.62	0.0405
HER3 < 50 th percentile (n = 35, 26)	1.4 mo	5.3 mo	0.32	0.0002
HER3 > 50 th percentile (n = 24, 37)	5.5 mo	2.8 mo	1.68	0.0844

Makhija S et al. *J Clin Oncol* 2010;28(7):1215-23.

SELECT PUBLICATIONS

Agus DB et al. **Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer.** *J Clin Oncol* 2005;23(11):2534-43.

Audeh MW et al. **Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: A proof-of-concept trial.** *Lancet* 2010;376(9737):245-51.

Bookman MA et al. **Evaluation of monoclonal humanized anti-HER2 antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of HER2: A phase II trial of the Gynecologic Oncology Group.** *J Clin Oncol* 2003;21(2):283-90.

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Gordon MS et al. **Clinical activity of pertuzumab (rhuMAb 2C4), a HER dimerization inhibitor, in advanced ovarian cancer: Potential predictive relationship with tumor HER2 activation status.** *J Clin Oncol* 2006;24(26):4324-32.

Makhija S et al. **Clinical activity of gemcitabine plus pertuzumab in platinum-resistant ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.** *J Clin Oncol* 2010;28(7):1215-23.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In which of the following clinical settings do PARP inhibitors have the potential to provide benefit in ovarian cancer (OC)?
 - a. BRCA1 germline mutation
 - b. BRCA2 germline mutation
 - c. BRCAness phenotype
 - d. All of the above
2. Which of the following groups of patients with OC participated in the GOG-0218 study, in which concurrent chemotherapy/bevacizumab followed by bevacizumab maintenance resulted in improved progression-free survival (PFS)?
 - a. Patients with chemotherapy-naïve disease
 - b. Patients with relapsed, platinum-sensitive disease
 - c. Patients with relapsed, platinum-refractory disease
 - d. All of the above
3. Which of the following has been shown in the GOG-0172 Phase III trial comparing IP chemotherapy to intravenous chemotherapy for Stage III OC?
 - a. Improvement in PFS
 - b. Improvement in overall survival
 - c. Both a and b
 - d. None of the above
4. Which supportive care strategy is important when considering IP chemotherapy?
 - a. Hydration
 - b. Patient education
 - c. Growth factor support
 - d. All of the above
5. Among patients with platinum-sensitive recurrent OC, the CALYPSO trial has shown that carboplatin/pegylated liposomal doxorubicin improves PFS by approximately two months compared to carboplatin/paclitaxel.
 - a. True
 - b. False
6. Which of the arm(s) in GOG-0218, a Phase III trial of chemotherapy versus chemotherapy/bevacizumab with or without maintenance bevacizumab as primary treatment for advanced OC, has demonstrated a statistically significant improvement in PFS compared to chemotherapy alone?
 - a. Chemotherapy with concurrent bevacizumab
 - b. Chemotherapy with concurrent bevacizumab and maintenance bevacizumab
 - c. Both a and b
 - d. None of the above
7. The incidence of gastrointestinal perforation and fistula was _____ on both treatment arms containing bevacizumab in the GOG-0218 trial.
 - a. Less than three percent
 - b. More than five percent
8. Konstantinopoulos and colleagues defined a gene expression profile of BRCAness that correlates with responsiveness to which of the following agents?
 - a. VEGF inhibitors
 - b. Platinum agents
 - c. PARP inhibitors
 - d. Both b and c
9. Which of the following is the mechanism of action of farletuzumab?
 - a. Inhibition of VEGF
 - b. Inhibition of folate receptor alpha
 - c. Inhibition of c-Kit
 - d. Inhibition of CD20
10. A combination of farletuzumab with carboplatin/paclitaxel in platinum-sensitive relapsed OC has shown a RECIST response of _____.
 - a. 30 percent
 - b. 70 percent
 - c. 99 percent

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Ovarian Cancer Update — Issue 1, 2010

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
GOG-0218: Chemotherapy versus chemotherapy/bevacizumab with or without maintenance bevacizumab as primary treatment for advanced ovarian cancer (OC)	4 3 2 1	4 3 2 1
Rationale for the development of farletuzumab as treatment for OC	4 3 2 1	4 3 2 1
Treatment algorithm for platinum-resistant and platinum-sensitive OC	4 3 2 1	4 3 2 1
Defining BRCAness and identifying patients who will benefit from PARP inhibitors	4 3 2 1	4 3 2 1
Use of IP and intravenous chemotherapy for optimally debulked Stage II or Stage III OC	4 3 2 1	4 3 2 1
Prospective US ovarian cancer screening study using the risk of OC algorithm	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

Yes No

If no, please explain:

Will this activity help you improve patient care?

Yes No Not applicable

If no, please explain:

Did the activity meet your educational needs and expectations?

Yes No

If no, please explain:

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Consider the utility of CA125 serum levels in monitoring disease progression and making treatment decisions. 4 3 2 1 N/M N/A
- Compare and contrast the risks and benefits of intraperitoneal and intravenous chemotherapy regimens when devising management strategies for optimally debulked Stage II or Stage III ovarian cancer. 4 3 2 1 N/M N/A
- Develop an evidence-based algorithm for the systemic treatment of recurrent platinum-sensitive and platinum-resistant ovarian cancer that optimizes long-term patient outcomes and quality of life. 4 3 2 1 N/M N/A
- Describe emerging data on the activity of poly(ADP-ribose) polymerase (PARP) inhibitors in patients with BRCA-like advanced ovarian cancer. 4 3 2 1 N/M N/A
- Summarize the existing data and ongoing clinical trials focused on angiogenesis inhibition in ovarian cancer, and identify patients who may benefit from this therapeutic approach. 4 3 2 1 N/M N/A
- Recall the rationale and activity of novel targeted agents under investigation for the treatment of ovarian cancer. 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with ovarian cancer about the availability of and participation in ongoing clinical trials. 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

What other practice changes will you make or consider making as a result of this activity?

What additional information or training do you need on the activity topics or other oncology-related topics?

Additional comments about this activity:

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- Yes, I am willing to participate in a follow-up survey.
- No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and editor for this educational activity

	4 = Excellent	3 = Good	2 = Adequate	1 = Suboptimal	
Faculty	Knowledge of subject matter				Effectiveness as an educator
Thomas J Herzog, MD	4	3	2	1	4 3 2 1
Deborah K Armstrong, MD	4	3	2	1	4 3 2 1
Robert A Burger, MD	4	3	2	1	4 3 2 1
Robert F Ozols, MD, PhD	4	3	2	1	4 3 2 1
Editor	Knowledge of subject matter				Effectiveness as an educator
Neil Love, MD	4	3	2	1	4 3 2 1

Please recommend additional faculty for future activities:

Other comments about the faculty and editor for this activity:

REQUEST FOR CREDIT — Please print clearly

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Ovarian Cancer™

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Ovarian Cancer™

U P D A T E

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