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Ovarian Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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Ovarian Cancer Update
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OVERVIEW OF ACTIVITY

Management of ovarian cancer (OC) includes optimal surgical debulking followed by postoperative chemotherapy and, in most cases, subsequent medical management when the disease recurs. Although many single-agent and combination chemotherapy regimens have been studied, only recently have antibody and small-molecule growth-inhibitory targeted agents been integrated into the OC 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 OC. To bridge the gap between research and patient care, this issue of *Ovarian Cancer Update* features one-on-one discussions with leading gynecologic oncology investigators. By providing information on the latest research developments in the context of expert perspectives, this activity assists medical and gynecologic oncologists with the formulation of therapeutic strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES

- Explain the rationale for angiogenesis inhibition in the treatment of OC.
- Summarize data from clinical trials that have evaluated anti-angiogenic agents in the management of OC.
- Describe how the most recent Phase III clinical trial data may affect the approach to OC.
- Consider the utility of CA125 levels in monitoring disease progression and making treatment decisions.
- Recall the rationale for and activity of novel targeted agents under investigation for the treatment of OC.
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate.

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INTERVIEW

Ursula A Matulonis, MD

Dr Matulonis is Medical Director and Program Leader of the Gynecologic Oncology Program and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

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Track 3 Arteriovenous thromboembolic events with bevacizumab in OC

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Select Excerpts from the Interview

Tracks 1-4

DR LOVE: Would you describe the Phase III GOG-0218 trial?

DR MATULONIS: The GOG-0218 trial was initiated a few years ago to evaluate chemotherapy with or without bevacizumab followed by maintenance bevacizumab for patients with ovarian cancer who underwent up-front debulking surgery (1.1). The trial enrolled more than 1,800 patients and involved three arms. This is an important study because it is the first time that a targeted therapy has been added to the backbone of up-front chemotherapy in ovarian cancer.

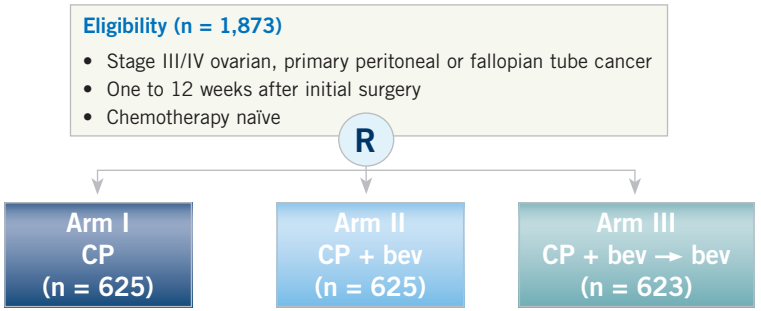
DR LOVE: What did they see in terms of outcomes?

DR MATULONIS: The bottom line is that no difference in progression-free survival (PFS) or overall survival was evident when chemotherapy alone was compared to chemotherapy administered with bevacizumab. However, when you compare chemotherapy alone to chemotherapy with bevacizumab followed by maintenance bevacizumab an improvement in PFS of approximately four months is observed, which was the goal of the study (Burger 2010; [1.2]).

I believe this is a trial in which we must watch the efficacy data over time and let them mature. When paclitaxel was initially added to the platinum agent, the change in PFS was six or eight months, but that translated into a year of overall survival benefit with longer follow-up. Therefore, we must watch this and see if longer follow-up might change the PFS data or if an overall survival difference might emerge.

1.1

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**.

1.2

GOG-0218 Study: 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

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

DR LOVE: Have you integrated these data into the up-front management of ovarian cancer?

DR MATULONIS: Certain patients will have contraindications, such as those with poorly controlled hypertension or those who would not be compliant in monitoring their blood pressure. I would caution patients who have a wound complication or those who underwent a bowel resection.

The trial was developed with a goal of identifying a four-month change in PFS, which is what occurred, so it does meet significance, and I believe a benefit exists. For the patients who are eligible to receive bevacizumab — such as those who have high-grade serous cancer or in whom disease is left behind after surgery — I certainly talk to them about the possibility of administering bevacizumab during chemotherapy and as maintenance therapy.

Tracks 7-8

DR LOVE: What about bevacizumab in recurrent ovarian cancer?

DR MATULONIS: I have no doubt that bevacizumab is effective in recurrent ovarian cancer (Burger 2007; Cannistra 2007). However, the risks — which are different in recurrent disease versus in the up-front setting — must be considered, especially in terms of gastrointestinal (GI) perforations. I tend to administer it to patients who have chemotherapy-resistant disease because another chemotherapy agent would have less utility.

Regarding the extent of disease, an ideal patient should have nodal recurrence, such as a few para-aortic nodes or pelvic lymph nodes, and not have diffuse peritoneal disease.

Bevacizumab can shrink tumors and put a cap on tumor growth. It is an agent that patients can tolerate well for a while. Some of the original data sets provided evidence of a decrease in ascites with bevacizumab. However, our patient population has changed, and currently we do not see many patients

with large-volume ascites, which may be attributable to the increased use of bevacizumab.

Tracks 9-11

DR LOVE: What are your thoughts on PARP inhibitors for the treatment of ovarian cancer?

DR MATULONIS: The data on PARP inhibitors that caught my attention were from the study of olaparib for patients with ovarian cancer with or without BRCA mutations (Gelmon 2010). It is a well-designed trial and provided objective evidence that patients without BRCA mutations could respond to a PARP inhibitor as monotherapy. This opens up the field of PARP inhibitors for a broader population of patients with ovarian cancer.

Another PARP inhibitor, iniparib, is being evaluated in ovarian cancer in ongoing Phase II trials with carboplatin/gemcitabine for platinum-sensitive and platinum-resistant ovarian cancer (1.3).

DR LOVE: Would you discuss the data comparing carboplatin/gemcitabine to carboplatin/paclitaxel in the initial management of ovarian cancer?

DR MATULONIS: The oral presentation at ASCO 2010 compared carboplatin/gemcitabine to carboplatin/paclitaxel as up-front induction treatment for ovarian cancer. For patients who achieved complete responses, they administered maintenance therapy after initial induction treatment.

The bottom line is that no difference was observed between carboplatin/gemcitabine and carboplatin/paclitaxel in the initial management of ovarian cancer (Teneriello 2010; [1.4]).

I believe that carboplatin/paclitaxel remains the standard, but now we have alternatives and therefore flexibility in treatment approach. If a patient either develops a significant reaction to paclitaxel or prefers to avoid alopecia, for example, in those settings carboplatin/gemcitabine could be used up front. ■

1.3 Ongoing Trials of Iniparib (BSI-201) in Advanced Ovarian Cancer

Clinicaltrials.gov identifier	Phase	N	Eligibility	Treatment
NCT01033123	II	41	One prior platinum-containing regimen; platinum sensitive	Carboplatin, gemcitabine, iniparib
NCT01033292	II	48	One prior platinum-containing regimen; platinum resistant	Carboplatin, gemcitabine, iniparib
NCT00677079	II	35	One prior platinum-containing regimen; confirmed BRCA1/2	Iniparib

www.clinicaltrials.gov, January 12, 2011.

1.4

Phase III Study Comparing Carboplatin/Paclitaxel (TC) to Carboplatin/Gemcitabine (GC) as Up-Front Induction Therapy for Ovarian Cancer (N = 831)

	TC	GC	*p*-value
Median progression-free survival	22.2 months	20.0 months	0.199
Overall response (CR + PR)	71.1%	67.6%	0.771
Complete response (CR)	43.9%	41.0%	0.795
Partial response (PR)	27.2%	26.6%	—
Stable disease (SD)	14.0%	15.8%	—
Disease control rate (CR + PR + SD)	85.1%	83.5%	>0.999
Select adverse events			
Grade 3 or 4 anemia	7.6%	27.4%	0.0001
Grade 3 or 4 thrombocytopenia	11.8%	67.7%	0.0001
Platelet transfusion	0%	2.7%	0.0009
Grade 2 or higher neuropathy	14.0%	2.2%	<0.0001
Grade 2 or 3 alopecia	51%	7.3%	<0.0001

Teneriello MG et al. *Proc ASCO* 2010;**Abstract LBA5008**.

SELECT PUBLICATIONS

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.

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.

Fong PC et al. **Poly(ADP)-ribose polymerase inhibition: Frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval.** *J Clin Oncol* 2010;28(15):2512-9.

Gelmon KA et al. **Can we define tumors that will respond to PARP inhibitors? A phase II correlative study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer.** *Proc ASCO* 2010;**Abstract 3002**.

Han ES et al. **Predictive and prognostic angiogenic markers in a Gynecologic Oncology Group phase II trial of bevacizumab in recurrent and persistent ovarian or peritoneal cancer.** *Gynecol Oncol* 2010;119(3):484-90.

Teneriello MG et al. **Phase III trial of induction gemcitabine (G) or paclitaxel (T) plus carboplatin (C) followed by elective T consolidation in advanced ovarian cancer (OC): Final safety and efficacy report.** *Proc ASCO* 2010;**Abstract LBA5008**.

INTERVIEW

Bradley J Monk, MD

Dr Monk is a gynecologic oncologist in the Division of Gynecologic Oncology and the Department of Obstetrics and Gynecology at Creighton University School of Medicine at St Joseph's Hospital and Medical Center in Phoenix, Arizona.

Tracks 1-13

Track 1 **Case discussion:** A 54-year-old Ashkenazi Jew with a family history of breast cancer and OC undergoes complete resection of Stage III OC followed by IP chemotherapy and IV bevacizumab on a Phase III GOG trial

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Track 3 Postoperative treatment options after optimal debulking for Stage III OC

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Track 5 Activity of PARP inhibitors in high-grade serous OC with or without BRCA mutation

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Track 7 Safety and efficacy of bevacizumab in the initial management of OC

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Track 9 Activity of bevacizumab monotherapy in relapsed/refractory OC

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Select Excerpts from the Interview

Track 5

DR LOVE: What are your thoughts on PARP inhibitors in ovarian cancer?

DR MONK: From my perspective, PARP inhibition is a breakthrough in targeted therapy for ovarian cancer (Audeh 2010; [2.1]).

Data have recently been presented providing evidence that PARP inhibitors have activity not only in patients with BRCA mutations but also in patients who are BRCA germline normal (Gelmon 2010). It is interesting that the phenotype of high-grade serous tumors, without germline BRCA mutations, correlates with considerable BRCA dysfunction. In fact, the level of BRCA dysfunction may be greater in the high-grade serous ovarian cancer setting than in the triple-negative breast cancer phenotype.

2.1

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 3/4 nausea[1]	Grade 3/4 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 of complete response, partial response or stable disease for ≥8 weeks

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

Tracks 7, 9

DR LOVE: What are your thoughts about the results of the GOG-0218 study of bevacizumab?

DR MONK: It has been almost six years since I began using bevacizumab for patients with recurrent ovarian cancer. I believe that anti-angiogenic therapy is effective in ovarian cancer and is the first real breakthrough of targeted agents in this cancer type. GOG-0218 is a positive trial, and I recommend up-front incorporation of bevacizumab to my patients and have seen this agent work in this setting.

DR LOVE: What are your thoughts on bevacizumab toxicity, particularly in patients with GI resections?

DR MONK: The incidence of bowel resection is decreasing overall in ovarian cancer. It probably occurs in 10 to 15 percent of patients. I am fine with using bevacizumab for patients who have undergone GI resections, as we have a lot of data on the safety of bevacizumab after bowel resection in colon cancer. A paper on this issue will be published from the GOG-0218 trial data also.

I always counsel my patients that proteinuria and hypertension are common and almost always occur with bevacizumab. However, they are not life threatening. The GOG-0218 study confirmed that the rates of potentially life-threatening complications such as thromboembolism are not very high (Burger 2010; [2.2]).

DR LOVE: What has been your experience using bevacizumab in later lines of treatment for ovarian cancer?

DR MONK: Bevacizumab provides a durable tumor control rate for patients with relapsed ovarian cancer. In the GOG Phase II trial, approximately 40 percent of patients remained progression free for six months, with an objective response rate of approximately 20 percent.

This is a major breakthrough because only four other drugs have shown response rates in this range as single agents in platinum-resistant ovarian cancer: docetaxel, paclitaxel, pemetrexed and nanoparticle albumin-bound (*nab*) paclitaxel. ■

2.2

GOG-0218 Study: 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 ≥2)*	1.2%	2.8%	2.6%
Hypertension (Grade ≥2)	7.2%	16.5%	22.9%
Proteinuria (Grade ≥3)	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 ≥3)	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**.

SELECT PUBLICATIONS

Abaid LN et al. **Bevacizumab, paclitaxel and carboplatin for advanced ovarian cancer: Low risk of gastrointestinal and cardiovascular toxicity.** *Eur J Gynaecol Oncol* 2010;31(3):308-11.

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.

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**.

Fong PC et al. **Poly(ADP)-ribose polymerase inhibition: Frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval.** *J Clin Oncol* 2010;28(15):2512-9.

Penson RT et al. **Phase II study of carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab as first-line chemotherapy for advanced mullerian tumors.** *J Clin Oncol* 2010;28(1):154-9.

Randall LM, Monk BJ. **Bevacizumab toxicities and their management in ovarian cancer.** *Gynecol Oncol* 2010;117(3):497-504.

Richardson DL et al. **Which factors predict bowel complications in patients with recurrent epithelial ovarian cancer being treated with bevacizumab?** *Gynecol Oncol* 2010;118(1):47-51.

INTERVIEW

Robert L Coleman, MD

Dr Coleman is Professor and Director of Clinical Research in the Department of Gynecologic Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-19

Track 1 Risk of Ovarian Cancer Algorithm (ROCA) as a feasible screening tool for OC

Track 2 Fertility preservation in patients with BRCA mutations without OC

Track 3 PARP as a therapeutic target in OC

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Track 5 BIBF 1120: A multitargeted tyrosine kinase inhibitor being investigated in the initial management of OC

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Track 7 Current approach to the incorporation of bevacizumab into the treatment of OC

Track 8 VEGF and angiogenesis in OC

Track 9 Farletuzumab: A humanized antibody targeting folate receptor alpha in OC

Track 10 **Case discussion:** A 55-year-old woman with Stage IV OC treated with neoadjuvant chemotherapy followed by surgical debulking

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Track 12 Principles of surgery in OC

Track 13 **Case discussion:** A 67-year-old woman with Stage IIIC OC has a complete response with initial systemic therapy and is followed with serial CA125 assessments

Track 14 Early treatment of relapsed OC based on CA125 level alone versus delayed treatment based on conventional clinical indicators

Track 15 Efficacy of carboplatin/gemcitabine in recurrent, platinum-sensitive OC

Track 16 Treatment algorithm for the management of OC

Track 17 **Case discussion:** A 62-year-old woman with OC experiences disease recurrence 10 months after initial therapy and then enrolls for a clinical trial investigating bevacizumab for platinum-sensitive disease

Track 18 Efficacy and side effects of paclitaxel versus docetaxel in OC

Track 19 Aflibercept as a novel anti-VEGF agent in OC

Select Excerpts from the Interview

Tracks 5-6

DR LOVE: What are your thoughts on the use of tyrosine kinase inhibitors (TKIs) such as BIBF 1120 in ovarian cancer?

DR COLEMAN: BIBF 1120 is an interesting compound. It is a multitargeted TKI that counts VEGF among its multiple targets. BIBF 1120 also has some fibroblast growth factor inhibition, which makes it interesting in the context of potential VEGF-independent growth.

The agent seems to be well tolerated overall (3.1). We didn't see a large number of patients coming off of the trial because of side effects or adverse events. Study of BIBF 1120 as maintenance therapy continues, and the agent is also moving forward into a first-line Phase III study for patients with platinum-sensitive disease.

3.1 **Randomized Placebo-Controlled Phase II Trial Evaluating BIBF 1120 as Maintenance Therapy After Treatment of Relapsed Ovarian Cancer**

	BIBF 1120 (n = 43)	Placebo (n = 40)	Hazard ratio	*p*-value
Efficacy				
Progression-free survival at 36 weeks	14.3%	5.0%	0.68	0.09
Adverse events				
Diarrhea	9%	2%	—	—
Vomiting	5%	2%	—	—
Hypertension	5%	0%	—	—
Elevated LFTs	51%	7%	—	—

Ledermann JA et al. *Proc ASCO* 2009;**Abstract 5501**.

Track 9

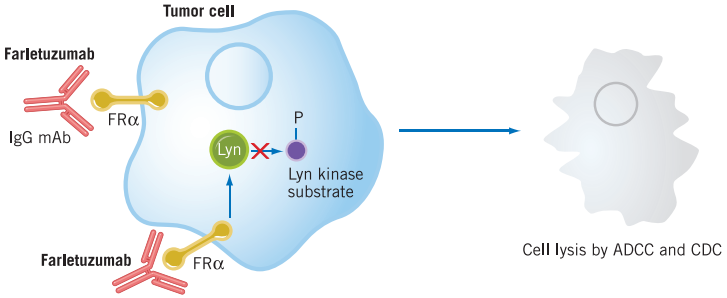
DR LOVE: What are your thoughts on the humanized monoclonal antibody farletuzumab?

DR COLEMAN: Farletuzumab targets the folate receptor alpha, which is overexpressed in more than 90 percent of ovarian cancer cells and is relatively absent in other cells. This makes farletuzumab a selective agent and a candidate for administration alone or in combination with chemotherapy for patients with ovarian cancer. We expect the agent would have low additional toxicity.

The mechanism of action seems to function through complement-dependent and antibody-dependent cytotoxicities (3.2).

3.2

Farletuzumab: Bimodal Mechanism of Action



Farletuzumab, a humanized monoclonal antibody (mAb), demonstrates a high affinity to the folate receptor alpha (FRα). Binding of mAb to FRα 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**.

DR LOVE: How does farletuzumab's effect compare to some of the antifolate chemotherapy agents, and could they be administered together?

DR COLEMAN: You could administer these agents together as they work on different axes. Other antifolate agents act on the enzymes involved with folate metabolism, so they work through a completely different mechanism of action. At ASCO 2010, our group presented Phase II trial data on farletuzumab (White 2010; [3.3]). An interesting take-home message from the presentation was the fact that when patients received farletuzumab in combination with the chemotherapy they received in the first-line setting, 20 to 25 percent fared better when farletuzumab was added to their chemotherapy backbone. So their secondary platinum-free interval was longer than their first. I'm extremely interested in evaluating the data that I hope will emerge from the combinations of farletuzumab with paclitaxel because we do see some impressive synergy with farletuzumab and the taxanes.

3.3

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

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

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

Track 19

DR LOVE: Would you describe the novel anti-VEGF agent aflibercept, or VEGF Trap, and compare its mechanism of action to that of bevacizumab?

DR COLEMAN: Aflibercept, or VEGF Trap, was designed as a fusion protein to essentially bind the VEGF binding domains of VEGFR1 and VEGFR2 into a fusion decoy receptor. Aflibercept has an IgG base, but it has the second domain of VEGFR1 and the third domain of VEGFR2, which provides an exquisite affinity for VEGF.

Aflibercept has a number of similarities to bevacizumab in that it targets VEGF, but it also has some differences. One of the major differences between the two compounds is that aflibercept binds VEGF one to one, whereas bevacizumab, being a monoclonal antibody, can bind several molecules at the same time.

Whether that will change the toxicity profile — for instance, with regard to clotting — is difficult to predict. A Phase II trial (NCT00436501) we are conducting with aflibercept is approaching completion, and so far, from our experience the toxicity profiles appear similar — hypertension, neurological symptoms and renal symptoms. ■

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INTERVIEW

William P McGuire, MD

Dr McGuire is Director of the Harry and Jeanette Weinberg Cancer Institute at Franklin Square Hospital Center and Clinical Professor of Medicine and Oncology at Georgetown University School of Medicine in Washington, DC.

Tracks 1-6

Track 1 Perspective on the efficacy and safety of bevacizumab in the GOG-0218 study

Track 2 Risks and benefits of chemotherapeutic options for recurrent, platinum-sensitive OC

Track 3 **Case discussion:** A 68-year-old woman is diagnosed with BRCA1 mutation-associated OC and undergoes optimal debulking surgery followed by IP chemotherapy

Track 4 Common emotional reactions among cancer survivors

Track 5 **Case discussion:** A 51-year-old woman diagnosed with advanced OC experiences long-term disease control with several combination chemotherapy regimens

Track 6 Patterns of metastases in OC

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss your thoughts on the GOG-0218 trial evaluating bevacizumab in ovarian cancer (Burger 2010; [1.1, 1.2])?

DR MCGUIRE: I believe that in the up-front setting we must show an overall survival advantage for a treatment to be justified, so to a patient I would say, "In the spirit of keeping you apprised, here's what's new" — but I tell the patient that the jury is still out regarding the use of bevacizumab. It is extraordinarily expensive unless their insurance company will pay for the drug. However, the drawbacks to using this drug are minimal.

One side effect of the drug, hypertension, can generally be controlled with a calcium channel blocker (Burger 2010; [2.2]). Some patients experience proteinuria, but few patients have developed proteinuria that required discontinuation of the drug.

The third concern, which is major, is bowel perforation. Initial studies showed bowel perforation rates from three to 11 percent in patients with recurrent, often large-volume disease. In the GOG-0218 study, we did not see an excessive number of bowel perforations in the group that received bevacizumab,

and the rates for Grade 2 or worse were less than three percent in all three groups.

Track 2

DR LOVE: How do you choose a regimen for a patient with recurrent platinum-sensitive disease?

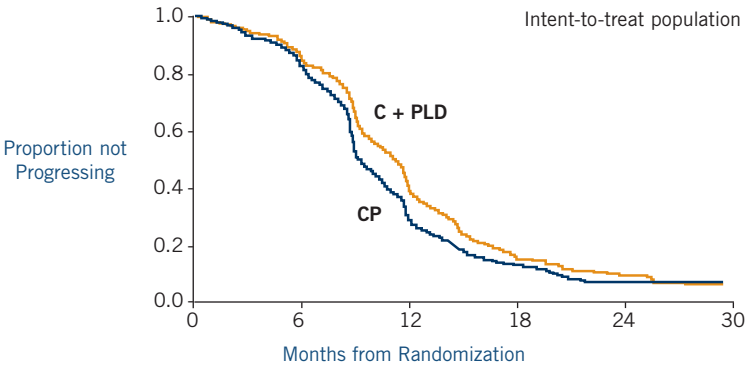
DR MCGUIRE: Of the platinum regimen choices, I rank the carboplatin/paclitaxel combination at the bottom of the list, primarily because of its toxicity profile. Many patients experience some degree of existing persistent neuropathy, and carboplatin/paclitaxel causes added neurotoxicity. Hair loss isn't a major concern from a toxicity standpoint, although it is important to a patient whose hair is recently beginning to regrow 12 months after primary therapy.

Carboplatin/gemcitabine does not cause neuropathy or hair loss, but it carries some hematologic toxicity that affects platelets and causes some respiratory events — shortness of breath without pulmonary infiltrates — that can be bothersome.

Carboplatin/pegylated liposomal doxorubicin is an agreeable regimen because it doesn't cause neuropathy. It doesn't cause hair loss or significant blood count suppression, and it is administered every four weeks rather than every three

4.1

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



In C + PLD arm, PLD dose was 30 mg/m^2

	C + PLD	CP	Hazard ratio	*p*-value (superiority)	*p*-value (noninferiority)
Median PFS, mo	11.3	9.4	0.82	0.005	<0.001

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

weeks. Therefore, for the patient who has recurrent platinum-sensitive disease and is still active, carboplatin/pegylated liposomal doxorubicin is probably the least noxious of the three regimens. Carboplatin/pegylated liposomal doxorubicin has been compared to carboplatin/paclitaxel and was found to significantly increase PFS (Pujade-Lauraine 2009; [4.1]). No one has compared carboplatin/pegylated liposomal doxorubicin to carboplatin/gemcitabine, but I'm reasonably certain that from a hematologic toxicity standpoint it would be easier to administer carboplatin/doxorubicin.

Track 6

DR LOVE: Can you discuss the clinical pattern of metastasis in ovarian cancer?

DR MCGUIRE: We usually see metastases in the lung, pleura, mediastinum and supraclavical lymph nodes. Metastasis in the brain or bone is extremely uncommon. In 30-plus years of practice, I've seen a total of three patients with brain metastases and one or two patients who had documented bony metastatic disease.

The disease tends to stay in the abdominal cavity, retroperitoneal nodes, splenic hilum and porta hepatis. Occasionally you see hepatic parenchymal metastases. More typically, these lesions are referred to as liver metastases, but that is not what they are. They are implants on Glisson's capsule. At times, the implants indent Glisson's capsule and make it seem as though a true parenchymal metastasis is present in the liver, but it is only a superficial metastasis that's indenting the liver. ■

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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**.

Rose PG et al. **Metastatic patterns in histologic variants of ovarian cancer. An autopsy study.** *Cancer* 1989;64(7):1508-13.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The primary endpoint in the Phase III GOG-0218 trial, reported at ASCO 2010, investigating bevacizumab in the up-front management of ovarian cancer was _____.**
   a. Complete response rate
   b. Overall response rate
   c. PFS
   d. Overall survival

2. **Which of the three arms in the GOG-0218 study showed superiority compared to the other arms in improving PFS?**
   a. Carboplatin/paclitaxel
   b. Carboplatin/paclitaxel/bevacizumab
   c. Carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance
   d. None of the above

3. **As single agents, PARP inhibitors have shown activity in _____.**
   a. BRCA1 mutation-positive ovarian cancer
   b. BRCA2 mutation-positive ovarian cancer
   c. BRCA germline-normal ovarian cancer
   d. Both a and b
   e. All of the above

4. **In a Phase III study, carboplatin/paclitaxel resulted in superior _____ compared to carboplatin/gemcitabine for the up-front treatment of ovarian cancer.**
   a. PFS
   b. Overall response rate
   c. Complete response rate
   d. None of the above

5. **A Phase II trial evaluating BIBF 1120 as maintenance therapy after treatment for relapsed ovarian cancer reported an approximate _____ improvement in PFS at 36 weeks for patients receiving BIBF 1120 versus placebo.**
   a. Two percent
   b. 10 percent
   c. 30 percent

6. **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

7. **A combination of farletuzumab and carboplatin/paclitaxel in platinum-sensitive relapsed ovarian cancer has shown a RECIST response rate of 70 percent.**
   a. True
   b. False

8. **Which of the following is the mechanism of action of aflibercept?**
   a. Inhibition of VEGF
   b. Inhibition of folate receptor alpha
   c. Inhibition of c-Kit
   d. Inhibition of CD20

9. **The most common site(s) of metastases in patients with ovarian cancer include the _____.**
   a. Brain
   b. Bone
   c. Lung, pleura, mediastinum and supraclavicular lymph nodes

10. **The incidence of Grade 2 or higher GI events, including GI perforation, in the bevacizumab-containing arms (2 and 3) of the GOG-0218 study was _____.**
    a. Less than three percent
    b. Five to 10 percent
    c. More than 10 percent

11. **When compared to carboplatin/paclitaxel, the bevacizumab-containing arms of the GOG-0218 study showed a _____ rate of venous and arterial thromboembolic events.**
    a. Similar
    b. Higher
    c. Lower

Post-test answer key: 1c, 2c, 3e, 4d, 5b, 6b, 7a, 8a, 9c, 10a, 11a

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Ovarian Cancer Update — Issue 2

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 study: Efficacy of bevacizumab in the initial management of ovarian cancer	4 3 2 1	4 3 2 1
Incidence and risk factors for bevacizumab-associated GI perforation in ovarian cancer	4 3 2 1	4 3 2 1
Activity of PARP inhibitors in ovarian cancer with or without BRCA mutation	4 3 2 1	4 3 2 1
Phase II clinical data on farletuzumab in ovarian cancer	4 3 2 1	4 3 2 1
Clinical trials of BIBF 1120 in ovarian cancer	4 3 2 1	4 3 2 1
Thromboembolic events with the addition of bevacizumab in the initial management of ovarian cancer	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:

- Explain the rationale for angiogenesis inhibition in the treatment of OC. . . . . 4 3 2 1 N/M N/A
- Summarize data from clinical trials that have evaluated anti-angiogenic agents in the management of OC. . . . . 4 3 2 1 N/M N/A
- Describe how the most recent Phase III clinical trial data may affect the approach to OC. . . . . 4 3 2 1 N/M N/A
- Consider the utility of CA125 levels in monitoring disease progression and making treatment decisions. . . . . 4 3 2 1 N/M N/A
- Recall the rationale for and activity of novel targeted agents under investigation for the treatment of OC. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate. . . . . 4 3 2 1 N/M N/A

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
Ursula A Matulonis, MD	4 3 2 1	4 3 2 1
Bradley J Monk, MD	4 3 2 1	4 3 2 1
Robert L Coleman, MD	4 3 2 1	4 3 2 1
William P McGuire, MD	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:

.....

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Name: ..... Specialty: .....

Professional Designation:

⬭ MD ⬭ DO ⬭ PharmD ⬭ NP ⬭ RN ⬭ PA ⬭ Other .....

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Research To Practice designates this educational activity for a maximum of 2.75 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

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UPDATE

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