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Ovarian Cancer™ UPDATE

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

EDITOR

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INTERVIEWS

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CME Certified

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 primary chemotherapy and, for most patients, 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 ovarian cancer population — 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

- Recognize the contributory roles of the specialized interdisciplinary team in achieving best-practice surgical and medical outcomes for patients with ovarian cancer.
- Compare and contrast the risks and benefits of intraperitoneal and intravenous chemotherapy regimens when devising management strategies for patients with optimally debulked Stage II and 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 outcome and quality of life.
- Summarize the existing data and ongoing clinical trials focused on angiogenesis inhibition of ovarian cancer, and identify patients who may benefit from this therapeutic approach.
- Consider the utility of evaluating CA125 serum levels and radiographic monitoring of patients with ovarian cancer that is in a state of remission.
- Understand the potential role of the risk-adapted use of maintenance systemic therapy for patients with ovarian cancer who have demonstrated an initial treatment response.
- Recall the scientific rationale for molecular-targeted agents under active 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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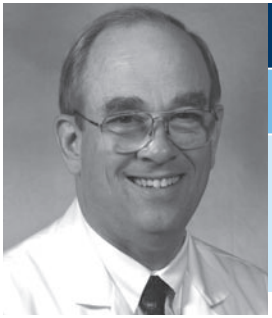

INTERVIEW

Tate Thigpen, MD

Dr Thigpen is Professor of Medicine and Director of Medical Oncology at the University of MS Medical Center in Jackson, Mississippi.

Tracks 1-12

Select Excerpts from the Interview

Track 1

DR LOVE: What important data sets in ovarian cancer were presented at ASCO this year?

DR THIGPEN: The most interesting abstract was the Japanese study evaluating weekly paclitaxel with every three-week carboplatin versus every three-week carboplatin/paclitaxel in women with advanced ovarian cancer (Isonishi 2008). The response rate was essentially equivalent — approximately 55 percent — for both arms, but the median progression-free survival was 28

months versus 17 months in the weekly and every three-week arms, respectively, which is a dramatic difference. There were not enough events for a final survival analysis, but two-year survival was 83 percent with weekly paclitaxel and 77 percent with the every three-week regimen, which was statistically significant.

These data fly in the face of data reported six years ago from a study that evaluated weekly versus every three-week single-agent paclitaxel as second-line therapy, which revealed no difference between the two schedules (Rosenberg 2002). However, the Japanese data do correspond with the observations in breast cancer that weekly paclitaxel may be the most effective schedule (Sparano 2008).

The Japanese study needs to be repeated before we can routinely introduce the regimen into clinical practice, and the Gynecologic Oncology Group is planning on conducting that study in the near future.

Tracks 3-4

DR LOVE: What are your thoughts about intraperitoneal (IP) therapy for ovarian cancer?

DR THIGPEN: This is a controversial topic. In January 2006, the National Cancer Institute declared a combination of IP therapy and intravenous (IV) therapy to be the standard treatment for small-volume residual advanced ovarian cancer. However, they couldn't recommend a specific regimen (NCI 2006).

At our institution, IP therapy remains an experimental technique that is generally not used outside of a clinical trial for several reasons. First, it's quite toxic and many patients are unable to tolerate it. In the last GOG study of IP therapy, 48 percent of the patients received three or fewer cycles of IP therapy and only 42 percent were able to complete six cycles (Armstrong 2006).

Second, we are not certain whether the addition of IP therapy is superior to IV carboplatin/paclitaxel. In all of the Phase III studies of IP therapy conducted in the United States to date, the control arm has been an IV cisplatin-based regimen. Yet evidence from the last GOG study comparing IV cisplatin/paclitaxel to IV carboplatin/paclitaxel showed that the latter might be superior (Ozols 2003).

To address this question, GOG is planning to begin a trial in the next six to 12 months comparing a control arm of IV carboplatin/paclitaxel to two IP regimens. One IP regimen will utilize cisplatin and the other carboplatin.

Track 7

DR LOVE: What studies have been conducted with bevacizumab for the treatment of advanced ovarian cancer?

DR THIGPEN: The initial Phase II study, GOG-0170D, evaluated bevaci-

zumab at 15 mg/kg every three weeks in patients who had received one or two prior chemotherapy regimens. The trial reported an objective response rate of 21 percent, a complete response rate of three percent and progression-free survival of at least six months in 40 percent (Burger 2007; [3.1, page 12]).

Two other Phase II studies evaluated bevacizumab in patients with more heavily pretreated disease. Among those patients who had received as many as three to five prior regimens, an increase in the complication rate was observed, specifically bowel complications (Cannistra 2007; Monk 2006). This suggests that if we use bevacizumab in ovarian cancer, it ought to be in the front-line setting or at first relapse.

DR LOVE: What about bevacizumab combined with chemotherapy?

DR THIGPEN: A trial evaluating cyclophosphamide with bevacizumab showed activity, but it was not a randomized study so we don't know whether the combination was better (Garcia 2008; [1.1]). Most of us feel strongly that administering bevacizumab with chemotherapy will be a better approach because of the possibility that it will improve the delivery of chemotherapy to the tumor by stabilizing the vasculature.

1.1

Phase II Trial of Bevacizumab and Low-Dose Metronomic Oral Cyclophosphamide in Recurrent Ovarian Cancer

"Our data suggest that the combination of bevacizumab and MC [metronomic chemotherapy] has significant activity in recurrent OC [ovarian cancer]. This was a population that was resistant to at least one line of platinum therapy having all progressed fewer than 12 months from a prior platinum therapy. The encouraging activity, time to progression, and median survival compare favorably with both conventional and investigational agents."

SOURCE: Garcia AA et al. *J Clin Oncol* 2008;26(1):76-82. **Abstract**

Tracks 8-10

DR LOVE: For patients with recurrent ovarian cancer, how do you define and approach platinum-sensitive versus platinum-resistant disease?

DR THIGPEN: Chemosensitive disease is defined as that which responded to the previous treatment and did not progress for at least six months. Patients with chemosensitive disease should be treated with a regimen that is the same or similar to the initial one because their chances of responding are good.

Disease that does not meet those criteria should be labeled as chemoresistant and should be treated with alternative drugs. For practical purposes, we talk about *platinum*-resistant or *platinum*-sensitive disease because all patients initially receive a platinum-based regimen. So patients who initially received paclitaxel/carboplatin and experience relapse more than six months later will fare better with a platinum-based regimen more so than anything else.

DR LOVE: How do you treat platinum-resistant, recurrent ovarian cancer?

DR THIGPEN: I prefer single agents in this setting because we don't have any proof that combinations are better. The six drugs that are commercially available, reimbursable and clearly have activity in platinum-resistant disease are pegylated liposomal doxorubicin (PLD), topotecan, gemcitabine, oral etoposide, weekly paclitaxel (if the patient received every three-week paclitaxel up front) and docetaxel.

All of these agents have response rates in the range of 15 to 20 percent and offer some survival benefit in the second-line setting. I generally start with PLD because it's administered once every four weeks, which is convenient for our patients. I use topotecan second, gemcitabine third, etoposide fourth, weekly paclitaxel fifth, and docetaxel sixth. Most of our patients will receive five or six different regimens.

There are two other agents that we should consider adding to that list — pemetrexed and bevacizumab. Bevacizumab, however, still has a question mark because of the increased complication rate among patients who have received multiple prior treatments. ■

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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. **Abstract**

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Rosenberg P et al. **Randomized trial of single agent paclitaxel given weekly versus every three weeks and with peroral versus intravenous steroid premedication to patients with ovarian cancer previously treated with platinum.** *Acta Oncol* 2002;41(5):418-24. **Abstract**

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INTERVIEW

Ursula A Matulonis, MD

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

Tracks 1-18

Select Excerpts from the Interview

Track 2

DR LOVE: What is your treatment approach for optimally debulked ovarian cancer?

DR MATULONIS: At the Dana-Farber/Harvard Cancer Center, patients with one centimeter or less of residual tumor after surgery either receive standard therapy — carboplatin/paclitaxel or IP cisplatin/paclitaxel — or enroll on a clinical trial.

We are conducting a pilot study evaluating IP carboplatin/paclitaxel with IV bevacizumab in women with newly diagnosed, optimally cytoreduced carcinoma of Müllerian origin. We also have a Phase II trial in which patients receive IV carboplatin/paclitaxel and bevacizumab for six months and then are randomly assigned to receive bevacizumab alone or bevacizumab in combination with erlotinib.

We have data with this combination in other tumors, and we know single-agent erlotinib has minor activity in recurrent ovarian cancer (Gordon 2005). Synergy may exist between these two biologic agents. In addition, high levels of EGFR expression occur in ovarian cancer cells.

We wouldn't expect erlotinib to do much for a patient with a large-volume recurrence. However, in the maintenance setting for a patient with small-volume disease, some of the anti-angiogenic effects of erlotinib might combine or perhaps synergize with bevacizumab to be beneficial.

Track 6

DR LOVE: How are you using bevacizumab in your practice?

DR MATULONIS: I don't use bevacizumab for patients with newly diagnosed ovarian cancer, but I do use it in recurrent disease. I select patients carefully and counsel them about the risks. I choose patients with a low risk of gastrointestinal perforation who are not hypertensive. I check their blood pressure and make sure they don't have any cardiovascular risk factors.

DR LOVE: When the ascites in a patient with refractory, advanced disease responds to bevacizumab, is that an antitumor effect, a vascular effect or both?

DR MATULONIS: When we see a reduction in ascites, we usually see concomitant decreases in peritoneal metastases, lymph node size and the areas of solid tumor growth. Although we can't be 100 percent certain, I believe it's an anticancer effect.

Track 9

DR LOVE: What are your thoughts about anti-HER2 therapy in ovarian cancer, including the potential role of pertuzumab?

DR MATULONIS: HER2 is not generally overexpressed in ovarian cancer, so we have to screen many cases to find the few that do overexpress HER2. Even in those patients with HER2 overexpression, the responses to trastuzumab are not particularly robust. Pertuzumab works differently than trastuzumab. Trastuzumab prevents HER2 signaling, while pertuzumab blocks HER2 receptor dimerization with HER3.

Three trials have evaluated pertuzumab in ovarian cancer. A single-agent study was published in the *Journal of Clinical Oncology* a number of years ago (Gordon 2006). A European Phase II trial evaluated a platinum-based chemotherapy regimen with or without pertuzumab in patients with platinum-sensitive disease (Kaye 2008). Another Phase II trial compared gemcitabine with or without pertuzumab in platinum-resistant ovarian cancer (Makhija 2007; [2.1]).

2.1

Phase II, Randomized, Placebo-Controlled, Double-Blind Trial of Gemcitabine with or without Pertuzumab for Patients with Platinum-Resistant Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Efficacy parameters	Gemcitabine + placebo (n = 65)	Gemcitabine + pertuzumab (n = 65)
Progression-free survival		
Median (range)	2.6 months (0-12.7)	2.9 months (0-8.7)
Adjusted HR (95% CI)	0.66 (0.43-1.03)	
Rate at 4 months	37%	48%
Overall response rate	5%	14%
Survival		
Median (range)	13.1 months (1.5-25.4)	12.0 months (1.3-23.9)
Adjusted HR (95% CI)	0.99 (0.60-1.62)	
Time to symptom deterioration (FOSI)		
Median (range)	1.7 (0-10.2)	3.8 (0-7.7)
Adjusted HR (95% CI)	0.62 (0.36-1.05)	

HR = hazard ratio; CI = confidence interval; FOSI = Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Symptom Index

SOURCE: Makhija S et al. *Proc ASCO* 2007;**Abstract 5507**.

Track 10

DR LOVE: Can you summarize the efficacy and toxicity associated with IP therapy?

DR MATULONIS: In the GOG-172 trial, comparing IV paclitaxel/cisplatin to IV paclitaxel with IP cisplatin/paclitaxel in patients with Stage III disease, the improvement in overall survival of approximately 16 months in the IP arm was the best we have seen so far (Armstrong 2006; [2.2]). The GOG-111 study, which added IV paclitaxel to IV cisplatin and compared it to IV cisplatin/cyclophosphamide in patients with Stage III/IV ovarian cancer, reported an approximately one-year improvement in overall survival (McGuire 1996).

The downside of IP therapy is the toxicity, which is greater than that associated with IV regimens, including increased neuropathy, pancytopenia, nausea, vomiting, renal toxicities and electrolyte problems. The side effects are

ameliorated somewhat by reducing the cisplatin dose to 75 mg/m^2, but that dose hasn't been tested in a randomized manner, so it can't be recommended uniformly for use.

2.2 **Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer**

"An intensive regimen of intravenous paclitaxel followed by intraperitoneal cisplatin and paclitaxel significantly improved progression-free survival (P = 0.05) and overall survival (P = 0.03) among women with newly diagnosed, optimally debulked stage III ovarian cancer. As compared with the intravenous-therapy group, women who received intraperitoneal treatment had a 25 percent reduction in the risk of death. Among all randomized phase 3 trials conducted by the GOG among patients with advanced ovarian cancer, the current trial yielded the longest median survival: 65.6 months, in the group of patients who received intraperitoneal therapy."

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

Track 14

DR LOVE: What is your clinical approach for patients with platinum-refractory ovarian cancer?

DR MATULONIS: Outside of a clinical trial, treatment options include using one of several cytotoxic agents or bevacizumab. I usually choose either topotecan or pegylated liposomal doxorubicin (PLD). I do not use the FDA-approved dose of PLD but a lower dose — 40 mg/m^2. The lower dose is more tolerable for patients in terms of the rash. Generally, if the rash becomes a problem one can reduce the dose or stretch the interval between cycles. If the rash is Grade II or worse, I generally drop the dose from 40 to 32 mg/m^2. ■

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Kaye SB et al. **A randomised phase II study evaluating the combination of carboplatin-based chemotherapy with pertuzumab (P) versus carboplatin-based therapy alone in patients with relapsed, platinum sensitive ovarian cancer.** *Proc ASCO* 2008;**Abstract 5520**.

Makhija S et al. **Results from a phase II randomized, placebo-controlled, double-blind trial suggest improved PFS with the addition of pertuzumab to gemcitabine in patients with platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer.** *Proc ASCO* 2007;**Abstract 5507**.

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. **Abstract**

INTERVIEW

Robert A Burger, MD

Dr Burger is Associate Professor of Clinical Obstetrics and Gynecology, Step II in the Department of Obstetrics and Gynecology's Division of Gynecologic Oncology at the University of California, Irvine Medical Center in Orange, California.

Tracks 1-12

Track 1	GOG-0170D: A Phase II study of bevacizumab in persistent or recurrent epithelial ovarian cancer or PPC
Track 2	Early clinical experience with bevacizumab in ovarian cancer
Track 3	VEGF expression in ovarian cancer
Track 4	Activity of single-agent bevacizumab in recurrent ovarian cancer
Track 5	Gastrointestinal perforation events in Phase II trials of bevacizumab
Track 6	Historical cohort studies of bevacizumab in heavily pretreated patients with ovarian cancer
Track 7	Clinical use of single-agent bevacizumab in advanced ovarian cancer
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Track 9	Caveats in the use of CA125 for monitoring disease progression in patients treated with anti-VEGF therapy
Track 10	Clinical algorithm for second- and later-line therapy in ovarian cancer
Track 11	Proposed Phase III trial of intraperitoneal chemotherapy in combination with bevacizumab for optimally debulked Stage III ovarian cancer
Track 12	Anticipated efficacy of adjuvant bevacizumab in ovarian cancer

Select Excerpts from the Interview

Tracks 1, 4-5

DR LOVE: Can you discuss the data from the GOG-0170D trial evaluating the use of bevacizumab for patients with persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer?

DR BURGER: Among 62 patients who had been previously treated with one or two cytotoxic regimens and had measurable disease by RECIST, bevacizumab led to a 21 percent objective response rate and a 40 percent progression-free survival of at least six months (Burger 2007; [3.1]).

A regression analysis performed at the conclusion of the trial factored in variables associated with disease progression in patients enrolled on Phase II trials of traditional cytotoxic agents: number of prior regimens, time from completion of initial therapy to first recurrence, age and performance status.

None of those factors predicted the time to disease progression in patients treated with bevacizumab (Burger 2007).

DR LOVE: Can you compare GOG-0170D to the other recently reported Phase II trial of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer (Cannistra 2007)?

DR BURGER: In GOG-0170D, the patients had received either one or two prior regimens. About 40 of the patients had experienced disease progression within six months of receiving their most recent platinum-containing regimen, and the remainder had a platinum-free interval greater than or equal to six months (Burger 2007). The other single-agent bevacizumab trial required that the patients' disease be either primarily or secondarily platinum-resistant, and they could have received two to three prior regimens (Cannistra 2007).

So regarding risk of disease progression with any therapy, the patients in the trial reported by Cannistra were at higher risk. In the trial by Cannistra, the objective response rate was 16 percent (Cannistra 2007). In GOG-0170D, the response rate was 21 percent (Burger 2007; [3.1]).

DR LOVE: What was observed in the two studies in terms of side effects and toxicity?

DR BURGER: The differences in toxicity were interesting. It's hard to compare across trials, but the trial by Cannistra was closed prematurely due to five cases of gastrointestinal perforation, and GOG-0170D had zero cases of gastrointestinal perforation.

3.1 **GOG-0170D: A Phase II Trial of Bevacizumab Monotherapy in Persistent or Recurrent Epithelial Ovarian Cancer or Primary Peritoneal Cancer (N = 62)**

Efficacy data

Response rate	21% (90% CI: 12.9-31.3%)
Complete response	3.2%
Partial response	17.7%
Stable disease	51.6%
Median duration of response	10.3 months
Progression-free survival (PFS) ≥ 6 months	40.3% (90% CI: 29.8-53.6%)

Conclusions

"In the second and third line treatment setting, patients with recurrent epithelial ovarian and primary peritoneal cancer, single agent bevacizumab:

- *Well tolerated at the dose and schedule of 15 mg/kg q21 days*
- *Active by clinical response and PFS"*

CI = confidence interval

SOURCE: Burger RA et al. *J Clin Oncol* 2007;25(33):5165-71. **Abstract**

In GOG-0170D, the rate of Grade III/IV proteinuria was minimal. Only one patient developed nephrotic syndrome, and it reversed after the discontinuation of bevacizumab. Approximately 10 percent of the patients had clinically relevant hypertension requiring antihypertensive therapy (Burger 2007). In the trial by Cannistra, no patients developed Grade III/IV proteinuria, but a number of patients with hypertension required therapy. Three patients experienced Grade III/IV arterial thrombotic events (Cannistra 2007).

Track 11

DR LOVE: Can you discuss evolving clinical research on the use of bevacizumab in combination with IP therapy?

DR BURGER: IP chemotherapy is considered a standard option for patients with Stage III ovarian cancer, especially those who have undergone optimal cytoreductive surgery. Three Phase III trials have demonstrated a survival advantage with IP regimens in combination with IV chemotherapy compared to standard IV chemotherapy regimens alone (Alberts 1996; Armstrong 2006; Markman 2001).

It's important to establish the safety and efficacy of these IP cytotoxic regimens in combination with bevacizumab. A Phase III trial is being developed to evaluate modified IP cytotoxic therapy in combination with bevacizumab for patients with Stage III, optimally debulked ovarian cancer. ■

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

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. **Abstract**

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. **Abstract**

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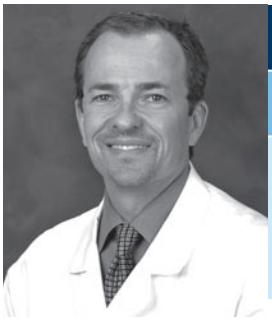


INTERVIEW

Bradley J Monk, MD

Dr Monk is Associate Professor and Director of Research in the Division of Gynecologic Oncology at the University of California, Irvine Medical Center's Chao Family Comprehensive Cancer Center in Orange, California.

Tracks 1-14

Select Excerpts from the Interview

Track 2

DR LOVE: What are some of the questions medical oncologists and gynecologic oncologists ask about the management of newly diagnosed ovarian cancer?

DR MONK: The standard up-front treatment for epithelial ovarian cancer is maximal surgical debulking followed by six courses of intravenous platinum- and taxane-based chemotherapy administered every three weeks. I believe that

guidelines have established the platinum drug as carboplatin at an area under the curve (AUC) between 5.0 and 7.5 mg/mL and the taxane as paclitaxel at a dose of 175 mg/m^2 administered over three hours (NCCN 2008).

However, questions then emanate and alter that standard. One can outline seven acceptable modifications: (1) using IP chemotherapy, (2) administering more than six cycles of chemotherapy, (3) using weekly chemotherapy, (4) substituting docetaxel as the taxane, (5) adding a targeted agent, specifically bevacizumab, (6) using reassessment surgery when the disease is in remission at the completion of adjuvant chemotherapy to confirm whether the tumor is in remission and (7) continuing chemotherapy during remission as maintenance or consolidation therapy.

Track 4

DR LOVE: What clinical trials are ongoing for patients in the up-front treatment setting?

DR MONK: One of the two scientific priorities being evaluated in the up-front treatment of epithelial ovarian cancer is the incorporation of bevacizumab. The GOG-0218 trial (4.1) adds bevacizumab to a platinum-and-taxane backbone. It also addresses maintenance bevacizumab in a third arm, even when the patient's disease is in remission.

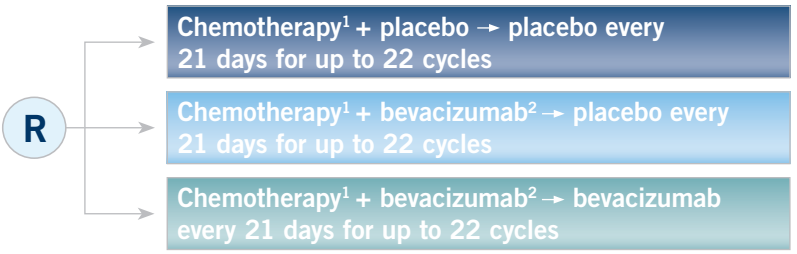
4.1

GOG-0218: A Phase III Study of Carboplatin/Paclitaxel (CP) versus CP/Bevacizumab with or without Extended Bevacizumab

Protocol IDs: GOG-0218, NCT00262847; Target Accrual: 2,000 (Open)

Eligibility

- Histologically confirmed Stage III with any gross residual disease OR Stage IV epithelial ovarian, primary peritoneal or fallopian tube cancer
- No prior chemotherapy for abdominal or pelvic cancer
- At least four weeks since major surgical procedure or open biopsy



[1] Chemotherapy = (IV paclitaxel 175 mg/m^2 + IV carboplatin AUC 6 mg/mL x min) every 21 days x 6 cycles

[2] Bevacizumab = 15 mg/kg every 21 days (beginning cycle 2)

SOURCES: NCI Physician Data Query, November 2008; Burger RA et al. *Proc ASCO* 2005;**Abstract 5009**.

The second scientific priority, also one of my seven controversies, is consolidation therapy. GOG-0212 (4.2) randomly assigns patients who are in remission to no treatment, 12 months of paclitaxel or 12 months of polyglutamate paclitaxel.

4.2

GOG-0212: A Phase III Randomized Trial of Paclitaxel versus Polyglutamate Paclitaxel as Consolidation/Maintenance Therapy versus No Further Anticancer Therapy until Disease Progression

Target Accrual: 1,100 (Open)

Eligibility

- Stage III/IV ovarian epithelial or primary peritoneal cancer
- Surgery
- Primary therapy: Five to eight courses of carboplatin (IV or IP) and paclitaxel or docetaxel

IV = intravenous; IP = intraperitoneal

SOURCE: NCI Physician Data Query, November 2008.

Track 8

DR LOVE: Could you discuss your research on trabectedin?

DR MONK: At the 2008 European Society of Medical Oncology meeting, I presented a trial with trabectedin — a DNA-active drug initially derived from the Caribbean sea squirt. I evaluated PLD with or without trabectedin in almost 700 patients. The combination demonstrated an improvement in

4.3

Randomized Phase III Trial of Trabectedin with Pegylated Liposomal Doxorubicin (PLD) versus PLD Alone in Women (N = 672) with Relapsed Recurrent Ovarian Cancer

	PLD + trabectedin	PLD alone	Hazard ratio	*p*-value
Median PFS				
All patients	7.3 months	5.8 months	0.79	0.019
Patients with PFI > 6 months	9.2 months	7.5 months	0.73	0.017
Response rate				
All patients	28%	19%	—	0.008
Patients with PFI > 6 months	35%	23%	—	0.004

PFS = progression-free survival; PFI = platinum-free interval

SOURCE: Monk BJ et al. ESMO Congress 2008;**Abstract LBA4**.

progression-free survival and response rate. Most of the benefit was observed in patients with chemotherapy-sensitive disease (Monk 2008; [4.3]).

Phase II trials of single-agent trabectedin have shown substantial activity in patients with chemotherapy-sensitive disease, with response rates between 30 and 40 percent. In patients with chemotherapy-resistant disease, the response rates were between five and 10 percent (Krasner 2007; Sessa 2005).

Tracks 11-12

DR LOVE: Would you discuss what you know about pertuzumab?

DR MONK: Pertuzumab is interesting because it is an antibody to HER3, which seems to be an important biomarker and target in epithelial ovarian cancer. Pertuzumab activity was demonstrated in the report of a randomized Phase II study of gemcitabine with or without pertuzumab (Makhija 2007; [2.1, page 9]). The final data from that study reported at ASCO 2008 suggested an association between efficacy and HER3 gene expression levels by RT-PCR (Amler 2008).

That endpoint was exploratory, so we question whether the evidence is sufficient or if we need to validate HER3 as a biomarker in a large prospective study before proceeding with studies of pertuzumab based on that biomarker. We need to study these agents in settings in which they will have the greatest likelihood of being effective, so I believe we should attempt to enrich the patient populations. We should use HER3 as a biomarker now to study pertuzumab. If the results are positive, the study should expand to a broader population. ■

SELECT PUBLICATIONS

Amler L et al. **HER pathway gene expression analysis in a phase II study of pertuzumab + gemcitabine vs gemcitabine + placebo in patients with platinum-resistant epithelial ovarian cancer.** ASCO 2008;**Abstract 5552**.

Burger RA et al. **Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer (EOC) or primary peritoneal cancer (PPC): A Gynecologic Oncology Group (GOG) study.** *Proc ASCO* 2005;**Abstract 5009**.

Krasner CN et al. **A Phase II study of trabectedin single agent in patients with recurrent ovarian cancer previously treated with platinum-based regimens.** *Br J Cancer* 2007;97(12):1618-24. **Abstract**

Makhija S et al. **Results from a phase II randomized, placebo-controlled, double-blind trial suggest improved PFS with the addition of pertuzumab to gemcitabine in patients with platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer.** ASCO 2007;**Abstract 5507**.

Monk BJ et al. **A randomized phase III study of trabectedin with pegylated liposomal doxorubicin (PLD) versus PLD in relapsed, recurrent ovarian cancer.** ESMO Congress 2008;**Abstract LBA4**.

National Comprehensive Cancer Network (NCCN®). **NCCN clinical practice guidelines in oncology. Ovarian cancer — Version 1. 2008.** Available at: **http://nccn.org/professionals/physician_gls/PDF/ovarian.pdf**.

Sessa C et al. **Trabectedin for women with ovarian carcinoma after treatment with platinum and taxanes fails.** *J Clin Oncol* 2005;23(9):1867-74. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In an ongoing Phase II trial at the Dana-Farber/Harvard Cancer Center, patients with ovarian cancer receive IV carboplatin/paclitaxel with bevacizumab for six months and then are randomly assigned to receive bevacizumab with or without _____.**
   a. Cetuximab
   b. Erlotinib
   c. Pertuzumab

2. **Which agent is believed to inhibit HER dimerization?**
   a. Cetuximab
   b. Pertuzumab
   c. Trastuzumab

3. **In GOG-172, comparing IV paclitaxel/cisplatin to IV paclitaxel with IP cisplatin/paclitaxel for patients with Stage III disease, overall survival was approximately _____ months longer for the patients receiving IP therapy.**
   a. Two
   b. Six
   c. 12
   d. 16

4. **In a Phase II trial (GOG-0170D) for patients with persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer, bevacizumab monotherapy resulted in a response rate of approximately _____.**
   a. Two percent
   b. Seven percent
   c. 21 percent
   d. 40 percent

5. **In GOG-0170D, which evaluated bevacizumab monotherapy for patients with recurrent ovarian cancer or primary peritoneal cancer, no cases of bowel perforations were reported.**
   a. True
   b. False

6. **GOG-0218 will evaluate the role of _____ in combination with paclitaxel/carboplatin for women with newly diagnosed Stage III/IV epithelial ovarian, primary peritoneal or fallopian tube cancer.**
   a. Bevacizumab
   b. Pertuzumab
   c. Trastuzumab
   d. Gemcitabine
   e. None of the above

7. **GOG-0212 will evaluate the role of _____ as consolidation/maintenance therapy for women with Stage III/IV epithelial ovarian or primary peritoneal cancer who have been treated with surgery and five to eight courses of primary chemotherapy.**
   a. Paclitaxel
   b. Polyglutamate paclitaxel
   c. Bevacizumab
   d. Both a and b
   e. Both a and c

8. **Which of the following agents has received FDA approval for the treatment of recurrent ovarian cancer?**
   a. Topotecan
   b. PLD
   c. Bevacizumab
   d. Both a and b
   e. All of the above

9. **The addition of trabectedin to _____ was found to improve progression-free survival and response rates for women with recurrent ovarian cancer.**
   a. Bevacizumab
   b. Topotecan
   c. PLD
   d. All of the above
   e. None of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Ovarian Cancer Update — Issue 3, 2008

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

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- **Management of platinum-resistant, recurrent ovarian cancer** 4 3 2 1
- **Toxicities associated with intraperitoneal therapy** 4 3 2 1
- **Role of anti-angiogenic and other targeted agents in the treatment of ovarian cancer** 4 3 2 1
- **Rationale for maintenance therapy in optimally debulked, Stage II/III disease** 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- **Management of platinum-resistant, recurrent ovarian cancer** 4 3 2 1
- **Toxicities associated with intraperitoneal therapy** 4 3 2 1
- **Role of anti-angiogenic and other targeted agents in the treatment of ovarian cancer** 4 3 2 1
- **Rationale for maintenance therapy in optimally debulked, Stage II/III disease** 4 3 2 1

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

☐ Yes ☐ 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 LEARNER statements by circling the appropriate selection:

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

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

- Recognize the contributory roles of the specialized interdisciplinary team in achieving best-practice surgical and medical outcomes for patients with ovarian cancer . . . . . 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 patients with optimally debulked Stage II and 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 outcome and quality of life . . . . . 4 3 2 1 N/M N/A
- Summarize the existing data and ongoing clinical trials focused on angiogenesis inhibition of ovarian cancer, and identify patients who may benefit from this therapeutic approach . . . . . 4 3 2 1 N/M N/A
- Consider the utility of evaluating CA125 serum levels and radiographic monitoring of patients with ovarian cancer that is in a state of remission . . . . . 4 3 2 1 N/M N/A
- Understand the potential role of the risk-adapted use of maintenance systemic therapy for patients with ovarian cancer who have demonstrated an initial treatment response . . . . . 4 3 2 1 N/M N/A
- Recall the scientific rationale for molecular-targeted agents under active 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

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 editor and faculty for this educational activity

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
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Ursula A Matulonis, MD	4 3 2 1	4 3 2 1
Robert A Burger, MD	4 3 2 1	4 3 2 1
Bradley J Monk, 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 editor and faculty for this activity:

.....

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Ovarian Cancer™

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