OCU | 2008 VOL 1 | ISSUE 1

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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LAUNCH ISSUE

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STATEMENT OF NEED/TARGET AUDIENCE

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 disease recurrence 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 recurrent ovarian cancer. In order to offer optimal oncology care to the ovarian cancer population — including the option of clinical trial participation — practicing medical and gynecologic oncologists must be well informed of these advances. To bridge the gap between research and patient care, *Ovarian Cancer Update* uses one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program will assist medical and gynecologic oncologists in the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Discuss the pathophysiology and epidemiology of localized, locally advanced and metastatic ovarian cancer.
- Critically evaluate the role of optimal surgical staging in the prognosis and subsequent medical management of epithelial ovarian cancer and borderline epithelial ovarian cancer.
- Review the risks and benefits of primary chemotherapy for patients with Stage II and III optimally debulked ovarian cancer, administered via the intraperitoneal or intravenous route, and the role of taxane-based chemotherapy regimens.
- Assess the application of emerging clinical trial data introducing new biologic agents and/or regimens into the management of recurrent platinum-sensitive and platinum-resistant ovarian cancer.
- Review and discuss the distinct mechanisms of action of biologic agents and other novel targeted signal transduction inhibitors specific to their application to ovarian malignancies.
- Describe and implement an algorithm for the treatment of patients in clinical complete remission who are found to have isolated increasing CA125 levels.
- Discuss the relative efficacy and adverse effects of acceptable recurrence modalities in the management of platinum-resistant metastatic or recurrent disease.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.

PURPOSE OF THIS ISSUE OF *OVARIAN CANCER UPDATE*

The purpose of Issue 1 of *Ovarian Cancer Update* is to support the learning objectives by offering the perspectives of Drs Ozols, Markman and Herzog on the integration of emerging clinical research data into the management of ovarian cancer.

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This program is supported by an educational grant from Genentech BioOncology.

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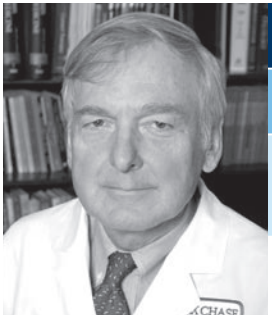

INTERVIEW

Robert F Ozols, MD, PhD

Dr Ozols is Senior Vice President of Medical Science at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

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Track 2	Treatment and prognosis of recurrent ovarian cancer
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DR LOVE: Can you review the key major trials in advanced ovarian cancer?

DR OZOLS: In a large Phase III trial conducted by the Gynecologic Oncology Group (GOG-158), carboplatin/paclitaxel was shown to be superior to cisplatin/paclitaxel and became the standard regimen (Ozols 2000). Patients do

experience hair loss and some neuropathy with this regimen, but it's effective and has a relatively favorable toxicity profile.

Studies were then conducted to determine whether adding a third drug to this regimen was beneficial, but a large GOG study (GOG0182-ICON5) with approximately 4,000 patients reported at ASCO showed that none of the three-drug regimens evaluated were better than the combination of paclitaxel and carboplatin (Bookman 2006).

Ongoing trials are comparing other combinations to paclitaxel/carboplatin, and additional studies have added a third drug, such as epirubicin (du Bois 2006), but none of them have been shown to improve survival as yet, compared to the gold standard.

DR LOVE: What do we know about biologic therapy in the treatment of ovarian cancer?

DR OZOLS: The GOG conducted a Phase II trial (GOG-170-D) of single-agent bevacizumab for previously treated patients with recurrent ovarian cancer, and the response rate was nearly 20 percent, and more than 35 percent of the patients did not have disease progression at six months (Burger 2005; [1.1]).

These data are striking because with other solid tumors, bevacizumab has been approved only in combination with chemotherapy. As a single agent, bevacizumab doesn't have much activity in breast, lung or colorectal cancer, but in ovarian cancer it appears to be particularly active. Consequently, a good deal

1.1 **GOG-170-D: A Phase II Trial of Bevacizumab Monotherapy in Persistent or Recurrent Epithelial Ovarian Cancer or Primary Peritoneal Cancer (N = 62)**

Efficacy data

Response rate	17.7%
Complete response	4.8% (90% CI: 10.3-27.7%)
Partial response	12.9%
Median duration of response	10.25 months
Stable disease	54.8%
Increasing disease	25.8%
Indeterminate	1.6%
Progression-free survival (PFS) ≥ 6 months	38.7% (90% CI: 28.3-49.9)

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. *Proc ASCO* 2005;**Abstract 5009**.

of interest has emerged in combining it with chemotherapy because, theoretically, it would potentiate the effects of chemotherapy as it does in the other tumor types, in addition to having its own activity.

Another interesting finding in the GOG-170-D trial was that no cases of gastrointestinal perforations were recorded. In a subsequent trial, approximately 10 percent of patients experienced this toxicity (Cannistra 2007), and if we pool all the data, it appears to occur in about five percent of patients.

Track 5

DR LOVE: Can you discuss the data from the GOG-0218 clinical trial evaluating bevacizumab combined with chemotherapy for previously untreated patients with advanced ovarian or primary peritoneal cancer?

DR OZOLS: The GOG-170-D trial of single-agent bevacizumab resulted in the launching of this Phase III trial in which patients are randomly assigned to paclitaxel/carboplatin with a placebo versus paclitaxel/carboplatin with concurrent bevacizumab versus paclitaxel/carboplatin/bevacizumab followed by maintenance bevacizumab for 14 months (1.2).

1.2

GOG-0218: A Phase III Randomized Study of Carboplatin and Paclitaxel versus Carboplatin, Paclitaxel and Concurrent 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 ovarian epithelial or primary peritoneal cancer
- No prior chemotherapy for abdominal or pelvic cancer
- At least four weeks since major surgical procedure or open biopsy

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

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

Study Contact

Gynecologic Oncology Group
Robert Burger, MD
Tel: 714-456-7971

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

This trial is evaluating whether bevacizumab potentiates the effects of chemotherapy and whether it is beneficial continued as maintenance therapy.

Track 7

DR LOVE: What are your thoughts about administering bevacizumab for recurrent ovarian cancer in clinical practice?

DR OZOLS: Bevacizumab is not approved for recurrent ovarian cancer, but it is used quite extensively in clinical situations. For patients who have ascites or pleural effusions, we've seen dramatic responses in improving these conditions — even if the solid tumor doesn't shrink — consequently sparing these patients a paracentesis or thoracentesis. That's an important quality-of-life issue, and I believe bevacizumab will be a valuable adjunct to the treatment of such patients.

We've had patients who aren't interested in participating in the GOG-0218 trial because they want to receive bevacizumab and don't want to take a chance of being assigned to a placebo arm. If the patient understands the cost and the risks that have been associated with this treatment, I believe using it in clinical practice is a reasonable approach.

In that setting, I would use bevacizumab concurrently with the chemotherapy because that's how it's been shown to be effective against other solid tumors. Also, given the long stabilization of disease observed in many patients in the GOG single-agent trial, I would continue it as maintenance therapy, if the patient was tolerating treatment and cost was not an issue.

Track 9

DR LOVE: What are the usual approaches to recurrent ovarian cancer?

DR OZOLS: For patients with platinum-sensitive disease, two regimens are currently being used. One is gemcitabine and carboplatin, which was recently approved by the FDA for platinum-sensitive disease on the basis of data from a randomized trial in Europe — a trial that evaluated carboplatin with or without gemcitabine and showed a three-month improvement in progression-free survival with the combination (Pfisterer 2006).

The other is paclitaxel and carboplatin. An earlier study — conducted by the ICON investigators in Europe, which evaluated carboplatin with or without paclitaxel in platinum-sensitive recurrent disease — likewise showed an improvement of three months in progression-free survival and a slight improvement in overall survival (Parmar 2003) with the combination.

In terms of efficacy, I believe these two regimens are equal. The difference is primarily in toxicity. With paclitaxel/carboplatin, patients experience hair loss, and if a patient is experiencing neuropathy from prior therapy, this regimen may exacerbate that toxicity. While gemcitabine/carboplatin doesn't exacer-

bate neuropathy, it is associated with more myelosuppression, but oncologists who use this combination frequently know how to minimize the consequences of this toxicity. This regimen is being used more frequently, and trials are now adding bevacizumab to see if that improves efficacy.

DR LOVE: What do we know about the role of anti-HER2 agents, such as trastuzumab and pertuzumab, in the treatment of recurrent ovarian cancer?

DR OZOLS: We initially thought that the overexpression of HER2 would be common in ovarian tumors, but in a large study, the GOG found that only approximately 10 percent of patients had disease that overexpressed HER2, and only a couple of responses to trastuzumab were recorded (Bookman 2003a). So trastuzumab by itself is not generally considered an active agent for ovarian cancer.

Pertuzumab is a monoclonal antibody that binds several sites on the different EGFR families. It's still too early to tell whether it will be a useful drug in ovarian cancer, but some responses were reported with it as monotherapy (Gordon 2006).

In 2007, data were presented at ASCO from a Phase II trial of gemcitabine with or without pertuzumab, and the combination appeared to have substantial activity (Makhija 2007; [1.3]). While the responses were relatively low, the data may be encouraging enough to continue a larger study. Also, there may be some markers for response to this regimen, so that study will be expanded. ■

1.3

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)	

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

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

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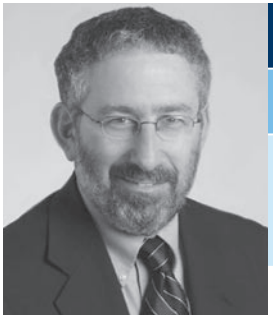


INTERVIEW

Maurie Markman, MD

Dr Markman is Vice President for Clinical Research at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-17

Select Excerpts from the Interview

Tracks 5-6

DR LOVE: You recently wrote an editorial about optimal surgical cytoreduction in the *Journal of Clinical Oncology* (Markman 2007). Can you discuss your thoughts?

DR MARKMAN: Ovarian cancer is an interesting malignancy from the perspective of its extraordinary sensitivity to chemotherapy, which has been recognized for a long time: 60 to 80 percent of patients achieve a major objective response. In fact, if one were to routinely perform second-look laparotomies

— this was done in the past and is not done now, but we have a lot of data on it — half of the women who had optimal residual ovarian cancer would have no evidence of disease at the time of the second-look surgical procedure.

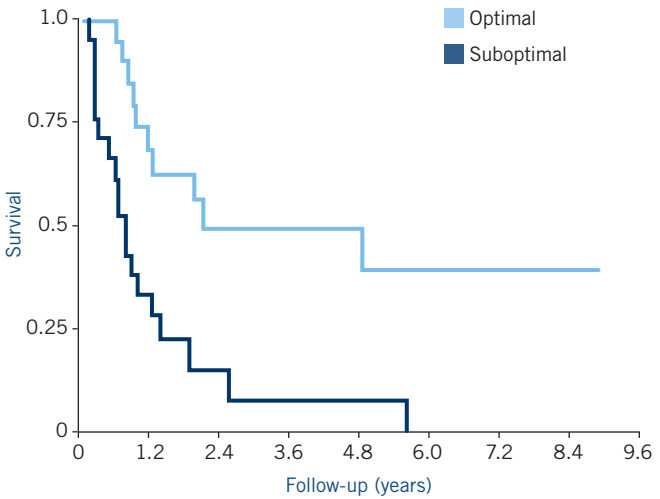
DR LOVE: Is this a pathologic complete response?

DR MARKMAN: Yes. So on the one hand, this is a remarkably chemotherapy-sensitive disease. On the other hand, the vast majority of these patients are not cured.

Because of the chemotherapy sensitivity and because of the fact that the disease was recognized many years ago as having a better prognosis when the disease was smaller at the start of chemotherapy (Griffiths 1975), the standard approach in the gynecologic cancer community has been to try to resect as much disease as possible prior to the administration of chemotherapy. Strong retrospective data support this (Sood 1998; Bristow 1999): If you review all of the studies' meta-analyses, you will find more favorable prognoses for women with the smallest

2.1

Retrospective Analysis of Survival Among 47 Patients with Stage III or IV Ovarian Cancer According to Residual Disease Following Cytoreduction



"We found significantly better survival in patients who had undergone optimal cytoreduction*. The value of optimal cytoreduction persisted even when only patients with advanced disease were considered ($P < 0.001$). The median survival for patients with optimal cytoreduction was 25 months compared with 8 months for those with suboptimal cytoreduction. In multivariate analysis, the amount of residual disease was the most significant prognosticator of survival ($P < 0.001$)."

* Optimal cytoreduction defined as < 1-cm residual tumor burden

SOURCE: Sood AK et al. *Cancer* 1998;82(9):1731-7. Copyright 2008 American Cancer Society. This material is reproduced with permission of Wiley-Liss Inc, a subsidiary of John Wiley & Sons Inc.
Abstract

volume of disease (including what is now called zero volume or no residual disease) before beginning chemotherapy (2.1).

The problem with all of these analyses is that no randomized trial has ever examined the question of chemotherapy alone versus chemotherapy followed by surgery — the so-called neoadjuvant approach — versus standard surgery followed by chemotherapy.

DR LOVE: Are there alternatives to up-front surgery for patients with ovarian cancer?

DR MARKMAN: The alternative would be to consider the neoadjuvant approach — making a diagnosis of ovarian cancer with laparoscopic surgery, followed by the use of effective chemotherapy, which currently includes a platinum and a taxane.

After three cycles of therapy in a responding patient, one could attempt surgical cytoreduction, then go on and administer further chemotherapy. This approach has been accepted by some surgeons but not by the majority in the US.

A prospective randomized trial addressing this question in Europe (EORTC-55971) has completed accrual. This EORTC study is evaluating a neoadjuvant approach versus surgery followed by chemotherapy (2.2).

It has shown no differences in outcome, so it may challenge the practice of performing aggressive surgery on all patients initially. From what I understand, we won't have the survival data for several years.

2.2

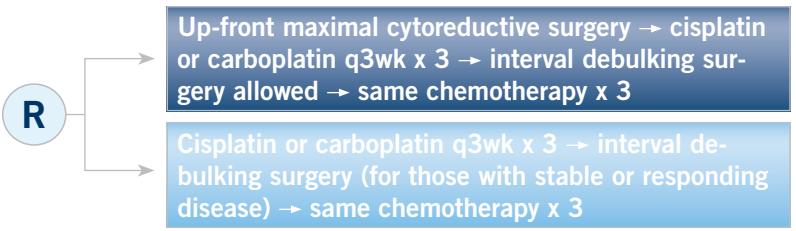
EORTC-55971: A Phase III Randomized Study of Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery versus Up-Front Cytoreductive Surgery with or without Interval Debulking Surgery

Protocol IDs: EORTC-55971, NCT00003636

Target Accrual: 740 (Closed)

Eligibility

- Histologically confirmed Stage IIIC or IV ovarian epithelial, peritoneal or fallopian tube carcinoma
- No prior surgical procedures other than diagnostic biopsy by laparotomy or laparoscopy
- Tumor > 2 cm (excluding ovaries) on laparoscopy or CT scan



SOURCE: NCI Physician Data Query, January 2008.

Track 10

DR LOVE: Would you discuss your thoughts on the mechanism of action of bevacizumab in ovarian cancer?

DR MARKMAN: A lot of speculation has occurred regarding why bevacizumab is so active in this tumor type (2.3). In particular, bevacizumab seems to be extremely effective in controlling malignant ascites (Byrne 2003; Hu 2005; Xu 2000; Wright 2006). Anecdotal data suggest that if you administer bevacizumab, the tumor may not shrink. So the effects of bevacizumab may not be associated with what you would consider an objective response, but the ascites is well controlled in some of these patients for a long time (2.4).

You often see tumor markers drop. The patients don't get better, but this raises the question of what we're observing with bevacizumab in ovarian cancer. In ovarian cancer, the hypothesis is that this is less of an effect on the cells directly and more of an effect on interstitial pressure of the tumor.

2.3

Rationale for the Effectiveness of Anti-Angiogenic Approaches in Ovarian Cancer

"If one had been asked 5 years ago to predict the tumors in which [a therapeutic benefit from anti-angiogenic approaches] would be most likely to be seen, there is no doubt that epithelial ovarian cancer would be very high on most lists. The reason relates to the biology of the disease. Angiogenesis, which is controlled by a range of pro-angiogenic factors, particularly including those in the vascular endothelial growth factor (VEGF) family of proteins, plays a central role in the physiological function of the healthy ovary. It could therefore be anticipated that the abnormal angiogenesis that characterizes malignancy would be especially relevant in this disease. Preclinical studies with appropriate models have indeed indicated the potential for an anti-VEGF strategy in preventing tumor progression and reducing the formation of malignant effusions. In addition, numerous studies indicate a direct correlation between angiogenic factors and disease extent and progression."

SOURCE: Kaye SB. *J Clin Oncol* 2007;25(33):5150–2. No abstract available

2.4

VEGF Has Been Implicated in the Development of Ascites

"…Various means of VEGF blockade have demonstrated very dramatic inhibitory effects on ascites formation. Thus, there is strong evidence that VEGF is a causative factor in the formation of ascites in at least some instances. Here we show not only that increased tumor expression of VEGF, using recently developed retroviral vectors, greatly accelerates the onset and amount of ascites but also that overexpression of VEGF alone in the peritoneum using adenoviral vectors, even in the absence of tumor, is adequate to cause ascites formation."

SOURCE: Byrne AT et al. *Clin Cancer Res* 2003;9(15):5721–8. **Abstract**

Bevacizumab seems to be additive to or synergistic with chemotherapy. If it decreases interstitial pressure in the tumor microenvironment, it allows high concentrations of drug to reach the tumor and could also cause more tumor cell kill. This is completely speculative, but it is an interesting hypothesis that makes some sense. ■

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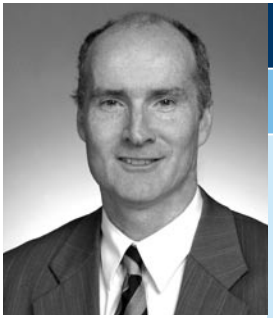


INTERVIEW

Thomas J Herzog, MD

Dr Herzog is Physicians and Surgeons Alumni Professor of Clinical Obstetrics and Gynecology and Director of the Division of Gynecologic Oncology at the National Cancer Institute Designated Comprehensive Cancer Center at Columbia University Medical Center in New York, New York.

Tracks 1-20

Track 1 GOG-111: Improved outcomes with cisplatin/paclitaxel compared to cisplatin/cyclophosphamide in suboptimal Stage III/IV ovarian cancer

Track 2 GOG-158: Cisplatin/paclitaxel versus carboplatin/paclitaxel in optimal Stage III epithelial ovarian cancer

Track 3 Involvement of medical oncologists in treating advanced ovarian cancer

Track 4 Patient outcomes after surgery performed by gynecologic oncologists versus OB/GYNs

Track 5 GOG-172: Intravenous versus intraperitoneal chemotherapy for optimal Stage III ovarian and primary peritoneal cancer

Track 6 Use of intravenous versus intraperitoneal chemotherapy by specialty and practice setting

Track 7 Catheter-related complications with intraperitoneal therapy

Track 8 Factors influencing the use of intravenous versus intraperitoneal chemotherapy

Track 9 Proposed GOG-606 trial of (neo)adjuvant intravenous chemotherapy in the elderly

Track 10 Rationale for the development of GOG-0218 incorporating bevacizumab with carboplatin/paclitaxel in Stage III or IV ovarian epithelial or primary peritoneal cancer

Track 11 Incidence and contributing factors of bevacizumab-related bowel perforation

Track 12 Eligibility and randomization in GOG-0218

Track 13 Development of a clinical trial to evaluate intraperitoneal chemotherapy and bevacizumab

Track 14 Time interval between administration of bevacizumab and surgery

Track 15 GOG-0213: Adjuvant carboplatin/paclitaxel with or without bevacizumab and/or secondary cytoreduction surgery in platinum-sensitive recurrent ovarian epithelial cancer, primary peritoneal cavity cancer or fallopian tube cancer

Track 16 Off-protocol use of bevacizumab for ovarian cancer

Track 17 Novel agents being evaluated in ovarian cancer, including pertuzumab

Track 18 Use of CA125 to monitor treatment and detect disease progression

Track 19 Time course and cause of death in ovarian cancer

Track 20 Chemosensitivity of ovarian cancer

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you review some of the key Gynecologic Oncology Group trials in ovarian cancer?

DR HERZOG: The GOG has published some landmark trials in the last 11 years. The first one that made a difference in practice was GOG-111, which substituted paclitaxel in place of cyclophosphamide in the cyclophosphamide/cisplatin regimen. A single-agent substitution resulted in a significant improvement in overall survival (McGuire 1996; [3.1]).

This study evaluated bulk-disease Stage III and Stage IV ovarian cancer. Remarkably, the median survival time went from 24 months to 38 months simply with that single-agent substitution. This introduced the taxane era into clinical practice for ovarian cancer.

The next landmark trial was GOG-158 (Ozols 2003). This trial was limited to patients with Stage III disease that was optimally debulked with less than 1-cm residual disease as the largest tumor after primary surgery.

They were randomly assigned to the winner of GOG-111 — an inpatient paclitaxel/cisplatin regimen in which the paclitaxel was administered over 24 hours — or a much more user-friendly outpatient regimen consisting of carboplatin with only a three-hour paclitaxel infusion.

No statistical difference appeared between the two arms (3.2). In fact, patients in the carboplatin arm fared a little better than those in the cisplatin arm.

3.1

GOG-111: A Phase III Study of Cyclophosphamide/Cisplatin versus Paclitaxel/Cisplatin in Stage III/IV Ovarian Cancer

Protocol ID: GOG-111
Accrual: 410

Eligibility

- Stage III ovarian cancer with large residual mass or Stage IV ovarian cancer

R → Paclitaxel/cisplatin
R → Cyclophosphamide/cisplatin

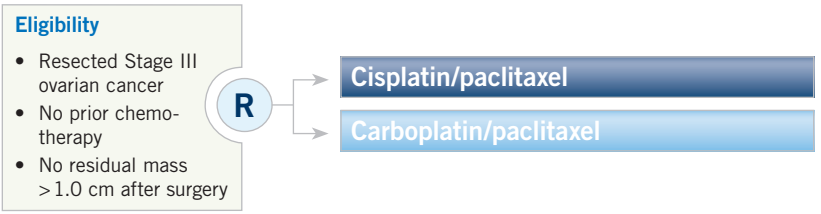
	Paclitaxel/ cisplatin (n = 184)	Cyclophosphamide/ cisplatin (n = 202)	Relative risk	*p*-value
Median progression-free survival	18 months	13 months	0.7	<0.001
Median overall survival	38 months	24 months	0.6	<0.001

SOURCE: McGuire WP et al. *N Engl J Med* 1996;334(1):1-6. **Abstract**

3.2

GOG-158: A Phase III Study of Cisplatin/Paclitaxel versus Carboplatin/Paclitaxel in Resected Stage III Ovarian Cancer

Protocol ID: GOG-158
Accrual: 792



Parameter	Carboplatin + paclitaxel	Cisplatin + paclitaxel	Relative risk (RR)
Median progression-free survival (PFS)	20.7 months	19.4 months	0.88
Median survival	57.4 months	48.7 months	0.84

"The results of this study demonstrate that the combination of carboplatin plus paclitaxel is not inferior to cisplatin plus paclitaxel with regard to PFS and survival in patients with small-volume stage III epithelial ovarian cancer. The RR of failure is 0.88 (95% CI, 0.75 to 1.03). The RR of death is 0.84 (95% CI, 0.70 to 1.02). This study was designed as a noninferiority trial and the results essentially exclude the possibility that the carboplatin regimen is inferior to the cisplatin regimen. This trial was not designed to determine whether the carboplatin regimen was superior to the cisplatin regimen. Nonetheless, the 16% reduced risk of death is of interest because it is suggestive that carboplatin may provide a slight increase in efficacy over cisplatin."

SOURCE: Ozols RF et al. *J Clin Oncol* 2003;21(17):3194-200. **Abstract**

Track 5

DR LOVE: What other advances have occurred through the GOG and other research entities?

DR HERZOG: The GOG-172 trial evaluated the role of administering a portion of the therapy intraperitoneally. We saw a median survival of 66 months for patients with Stage III disease who received a component of their care intraperitoneally versus 50 months for those who received only intravenous medication (Armstrong 2006; [3.3]).

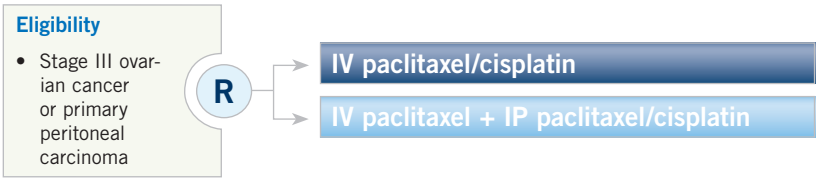
What does that tell you? First, that's a big difference in survival — almost 17 months. Second, in Stage III ovarian cancer, we now have median survivals that eclipse five years, which is most encouraging.

DR LOVE: What about bevacizumab and intraperitoneal therapy?

3.3

GOG-172: A Phase III Study of Intravenous (IV) versus Intraperitoneal (IP) Paclitaxel/Cisplatin in Stage III Ovarian Cancer

Protocol ID: GOG-172; Accrual: 429



	IV paclitaxel/ cisplatin (n = 210)	IV paclitaxel + IP paclitaxel/cisplatin (n = 205)	Relative risk	*p*-value
Median progression-free survival	18.3 months	23.8 months	0.80	0.05
Median overall survival	49.7 months	65.6 months	0.75	0.03

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

DR HERZOG: That's a question the GOG is trying to settle. We are substituting intraperitoneal carboplatin for cisplatin to see if we can reduce toxicity and make the regimen more user friendly. Then we're adding bevacizumab into that equation, so we're expecting a three-arm trial.

Track 16

DR LOVE: Do you see bevacizumab fitting into therapy off protocol right now?

DR HERZOG: The GOG-0213 trial was recently activated in the recurrent setting. This trial is complex in that it's trying to answer two questions in recurrent, platinum-sensitive ovarian cancer (3.4).

First, should you take these patients to the operating room and debulk the disease again? Patients who are candidates for surgery are randomly assigned to surgery or no surgery.

The second question is, what's the role of bevacizumab in that setting? Patients will be randomly assigned to carboplatin/paclitaxel alone or with bevacizumab followed by maintenance bevacizumab until disease progression. There's no defined endpoint to the bevacizumab.

Off protocol, we're seeing a lot of bevacizumab use. People are using it mostly in the recurrent setting based on the GOG-170-D data (Burger 2005). We are also seeing it used as a single agent, which has shown a 20-plus percent response rate.

DR LOVE: If someone with recurrent disease came to you for a second opinion, and she'd had bevacizumab recommended as a single agent, how would you respond?

DR HERZOG: It depends on where the patient is in the treatment queue, what she's received before and what kind of toxicities she's developed, but largely, I would agree with that recommendation. ■

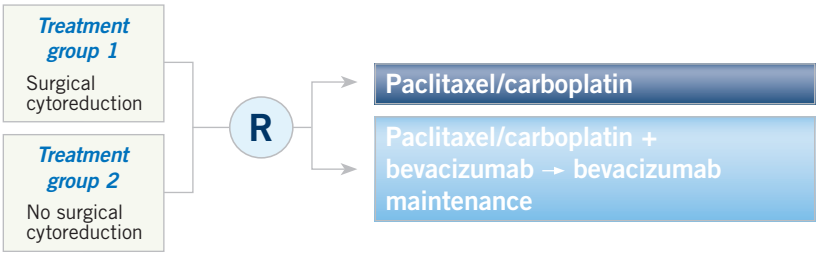
3.4

GOG-0213: A Phase III Study of Carboplatin and Paclitaxel with or without Bevacizumab After Surgery for Patients with Recurrent Ovarian Epithelial Cancer, Primary Peritoneal Cavity Cancer or Fallopian Tube Cancer

Protocol IDs: GOG-0213, NCT00565851; Target Accrual: 660 (Open)

Eligibility

- Recurrent ovarian, peritoneal cavity or fallopian tube cancer



Study Contact

Gynecologic Oncology Group
Robert Coleman, MD
Tel: 713-745-3357; 800-392-1611

SOURCE: NCI Physician Data Query, January 2008.

SELECT PUBLICATIONS

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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**

Ozols RF et al. **Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group study.** *J Clin Oncol* 2003;21(17):3194-200. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In a Phase II trial 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. Five percent
   c. 17 percent
   d. 40 percent

2. **The GOG-0218 Phase III trial evaluates carboplatin and paclitaxel with or without _____ for Stage III or IV ovarian epithelial or primary peritoneal cancer.**
   a. Erlotinib
   b. Gefitinib
   c. Imatinib
   d. Bevacizumab
   e. Cetuximab

3. **Data from a Phase II, randomized, placebo-controlled, double-blind trial of _____ with or without pertuzumab suggested that pertuzumab may add activity as reflected by improvements in progression-free survival.**
   a. Paclitaxel
   b. Paclitaxel/carboplatin
   c. Gemcitabine
   d. Gemcitabine/carboplatin

4. **In a Phase III clinical trial of intravenous paclitaxel/cisplatin versus intravenous paclitaxel with intraperitoneal paclitaxel/cisplatin, intraperitoneal therapy resulted in _____.**
   a. Improved survival
   b. Increased toxicities
   c. Both a and b
   d. None of the above

5. **The prognosis for women with ovarian cancer is improved if they have _____.**
   a. Small-volume residual disease
   b. Zero-volume or no residual disease
   c. Undergone optimal debulking surgery
   d. All of the above

6. **According to data from three randomized trials, survival advantages have been associated with the use of _____ therapy among patients with small-volume residual disease.**
   a. Intravenous
   b. Intraperitoneal
   c. Both a and b
   d. None of the above

7. **The landmark GOG-111 trial showed that progression-free survival and overall survival were significantly higher with paclitaxel/cisplatin compared to cyclophosphamide/cisplatin among patients with Stage III or IV ovarian cancer.**
   a. True
   b. False

8. **In the GOG-158 trial comparing carboplatin/paclitaxel to cisplatin/paclitaxel for patients with resected Stage III ovarian cancer, the efficacy data showed _____.**
   a. Cisplatin/paclitaxel to be significantly superior
   b. Carboplatin/paclitaxel to be significantly superior
   c. No statistically significant difference between the two arms

9. **The Phase III trial GOG-0213 is comparing carboplatin/paclitaxel with or without _____ with or without prior surgery for patients with recurrent ovarian epithelial, primary peritoneal cavity or fallopian tube cancer.**
   a. Bevacizumab
   b. Pertuzumab
   c. Imatinib

10. **In the GOG-170-D Phase II trial evaluating bevacizumab monotherapy in patients with recurrent ovarian cancer or primary peritoneal cancer, no incidences of bowel perforation were reported.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Ovarian Cancer Update — Issue 1, 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 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Staging at diagnosis for ovarian cancer..... 4 3 2 1

Role of anti-angiogenic and anti-HER2 agents in the treatment of ovarian cancer .. 4 3 2 1

Rationale for cytoreductive surgery for patients with ovarian cancer 4 3 2 1

Treatment options for recurrent ovarian cancer..... 4 3 2 1

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

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Staging at diagnosis for ovarian cancer..... 4 3 2 1

Role of anti-angiogenic and anti-HER2 agents in the treatment of ovarian cancer .. 4 3 2 1

Rationale for cytoreductive surgery for patients with ovarian cancer 4 3 2 1

Treatment options for recurrent ovarian cancer..... 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 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:

- Discuss the pathophysiology and epidemiology of localized, locally advanced and metastatic ovarian cancer. ..... 4 3 2 1 N/M N/A
- Critically evaluate the role of optimal surgical staging in the prognosis and subsequent medical management of epithelial ovarian cancer and borderline epithelial ovarian cancer. ..... 4 3 2 1 N/M N/A
- Review the risks and benefits of primary chemotherapy for patients with Stage II and III optimally debulked ovarian cancer, administered via the intraperitoneal or intravenous route, and the role of taxane-based chemotherapy regimens. ..... 4 3 2 1 N/M N/A
- Assess the application of emerging clinical trial data introducing new biologic agents and/or regimens into the management of recurrent platinum-sensitive and platinum-resistant ovarian cancer.. ..... 4 3 2 1 N/M N/A
- Review and discuss the distinct mechanisms of action of biologic agents and other novel targeted signal transduction inhibitors specific to their application to ovarian malignancies.. ..... 4 3 2 1 N/M N/A
- Describe and implement an algorithm for the treatment of patients in clinical complete remission who are found to have isolated increasing CA125 levels.. ..... 4 3 2 1 N/M N/A
- Discuss the relative efficacy and adverse effects of acceptable recurrence modalities in the management of platinum-resistant metastatic or recurrent disease. ... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of 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:

.....

.....

May we include you in future assessments to evaluate the effectiveness of this activity?

☐ Yes ☐ No

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

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Faculty	Knowledge of subject matter	Effectiveness as an educator
Robert F Ozols, MD, PhD	4 3 2 1	4 3 2 1
Maurie Markman, MD	4 3 2 1	4 3 2 1
Thomas J Herzog, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Degree:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ BS ☐ RN ☐ PA ☐ Other .....

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Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credit(s)™*. 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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Ovarian Cancer™

U P D A T E

This program is supported by an educational grant from Genentech BioOncology.

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Last review date: February 2008
Release date: February 2008
Expiration date: February 2009
Estimated time to complete: 3 hours