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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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Ovarian Cancer Update

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OVERVIEW OF ACTIVITY

Optimal oncologic management of ovarian cancer begins with intensive surgical staging and cytoreduction, followed by postoperative 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

- Consider the utility of evaluating CA125 serum levels in patients with ovarian cancer in a state of remission.
- Evaluate the investigation of biomarkers for prediction of response to biologic agents for the treatment of 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 in ovarian cancer, and identify patients who may benefit from this therapeutic approach.
- Consider the pros and cons of immediate adjuvant chemotherapy versus surgical staging followed by adjuvant chemotherapy when developing a treatment algorithm for patients with early incompletely staged ovarian cancer.
- Counsel appropriately selected patients with ovarian cancer about the availability of and participation in ongoing clinical trials.

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TABLE OF CONTENTS

INTERVIEWS

3 **Richard T Penson, MD, MRCP**
Assistant Professor of Medicine
Harvard Medical School
Clinical Director, Medical Gynecologic Oncology
Massachusetts General Hospital
Boston, Massachusetts

7 **Robert J Morgan, MD**
Director, Continuing Medical Education
Co-Director, Gynecologic and Peritoneal Malignancy Program
Department of Medical Oncology and Therapeutics Research
City of Hope
Duarte, California

11 **Don S Dizon, MD**
Assistant Professor, Obstetrics-Gynecology and Medicine
The Warren Alpert Medical School of Brown University
Director of Medical Oncology and Integrative Care
Co-Director, The Center for Sexuality, Intimacy and Fertility
Program in Women's Oncology
Women and Infants' Hospital
Providence, Rhode Island

15 **Robert S Mannel, MD**
Director, OU Cancer Institute
Professor and Chairman
Department of Obstetrics and Gynecology
The Rainbolt Family Chair in Cancer
The University of Oklahoma College of Medicine
Oklahoma City, Oklahoma

18 POST-TEST

19 EDUCATIONAL ASSESSMENT AND CREDIT FORM

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INTERVIEW

Richard T Penson, MD, MRCP

Dr Penson is Assistant Professor of Medicine at Harvard Medical School and Clinical Director of Medical Gynecologic Oncology at Massachusetts General Hospital in Boston, Massachusetts.

Tracks 1-9

Track 1 Development of poly(ADP-ribose) polymerase (PARP) inhibitors for ovarian cancer

Track 2 Investigation of tissue biomarkers predictive of response to PARP inhibitors

Track 3 Evaluating potential predictors of response to anti-angiogenic agents in ovarian cancer

Track 4 Randomized, controlled clinical trials of chemotherapy/bevacizumab for the up-front treatment of newly diagnosed (GOG-0218) or recurrent (OCEANS) ovarian cancer

Track 5 Role of bevacizumab for recurrent ovarian cancer outside of a clinical trial

Track 6 Incorporating bevacizumab into intraperitoneal chemotherapy regimens

Track 7 Molecular-targeted clinical studies with tyrosine kinase inhibitors (TKIs) for ovarian cancer

Track 8 MRC OV05/EORTC-55955: Early treatment of relapsed ovarian cancer based on CA125 level alone versus delayed treatment based on conventional clinical indicators

Track 9 CALYPSO: Carboplatin/pegylated liposomal doxorubicin versus carboplatin/paclitaxel in relapsed platinum-sensitive ovarian cancer

Select Excerpts from the Interview

Tracks 4-5

DR LOVE: Where are we right now in terms of clinical research on bevacizumab in ovarian cancer?

DR PENSON: The two current registration studies that are close to completion in ovarian cancer are GOG-0218 and the OCEANS study. GOG-0218 is an up-front study for patients with optimally or suboptimally cytoreduced ovarian cancer. Patients receive paclitaxel/carboplatin, paclitaxel/carboplatin and bevacizumab or paclitaxel/carboplatin and bevacizumab followed by one year of consolidation bevacizumab. Because this study is placebo controlled, progression-free survival can be used as the primary endpoint.

The OCEANS study is evaluating gemcitabine and carboplatin with or without bevacizumab for patients with platinum-sensitive or potentially platinum-sensitive recurrent disease. This also has a placebo-controlled design with treatment until progression of disease.

DR LOVE: Do you believe that a role currently exists for bevacizumab in ovarian cancer outside of a protocol setting?

DR PENSON: For recurrent disease, yes. The groundswell of opinion was codified by the NCCN publication that gave bevacizumab a preferred drug status, which allows it to be cited for reimbursement. I have many patients who have received bevacizumab for three years, not typically with only one drug but with a sequence of drugs. I don't believe a role exists for it as first-line therapy outside of a trial. A few patients have persuaded me to use it earlier, but only a few.

Track 7

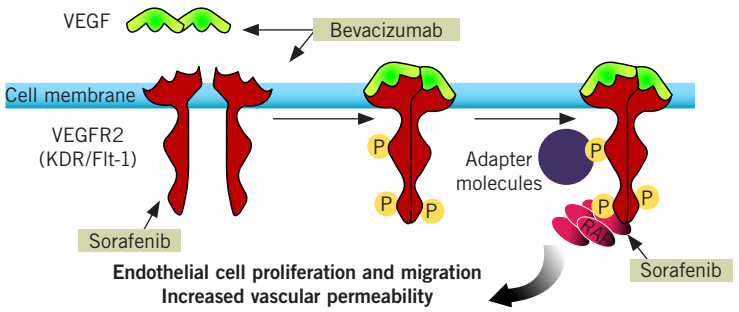
DR LOVE: What about other VEGF inhibitors, such as sunitinib, that are being evaluated in ovarian cancer?

DR PENSON: The convenience of having an oral daily medication is appealing, although IV infusion often allows for support from other patients in addition to the medical team. The TKIs are interesting because they have a broad spectrum of effects, which means that potentially multiple sites can be targeted.

We published a study with cediranib — an oral VEGF TKI — and observed a good response rate in the 20 percent range but with a lot of toxicity compared to bevacizumab (Matulonis 2009). We also have an ongoing study with sunitinib. The most interesting study evaluating VEGF inhibition was from Elise Kohn's group, in which they evaluated bevacizumab/sorafenib in patients with advanced solid tumors, and the response rate was approximately 40 percent, which is remarkable (Azad 2008).

According to these results, carefully selected patients can fare incredibly well when targeting a particular pathway with multiple agents (Azad 2008; [1.1]). I believe it makes sense to target multiple, key parallel pathways in trying to eradicate or control cancer.

1.1 **Targeting the VEGF Pathway with Bevacizumab in Combination with Sorafenib**



SOURCE: Originally published by the American Society of Clinical Oncology. Azad NS et al: *J Clin Oncol* 26(22), 2008: 3709-14.

Track 8

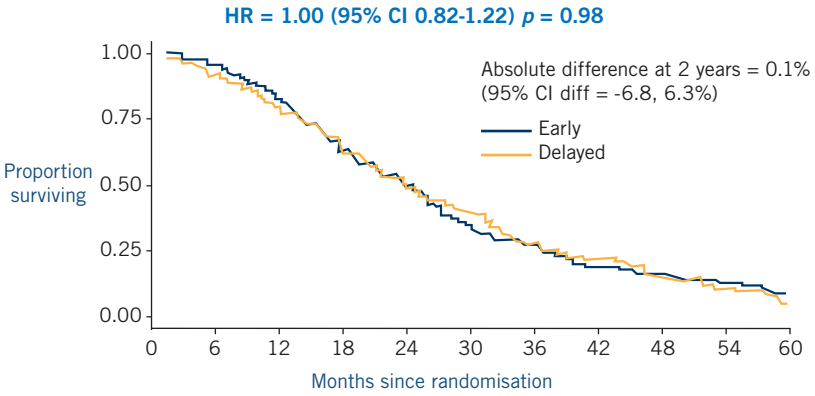
DR LOVE: What are your thoughts about the ASCO 2009 plenary presentation on CA125 screening in patients after surgery?

DR PENSON: Gordon Rustin presented this randomized controlled trial in which both the clinician and the patient were blinded to what was happening with the patients' CA125 levels. When CA125 increased, patients were randomly assigned in a one-to-one fashion to receive that information. On average, it took five months longer for patients in the control group to receive treatment. No difference in overall survival was evident between early and delayed second-line chemotherapy (Rustin 2009; [1.2]), and more importantly, a negative effect on quality of life was observed.

The unequivocal conclusion was that the cancerous clone isn't affected by early chemotherapy, and we can hurt patients with chemotherapy administered before they experience clinical progression of disease.

1.2

Overall Survival Outcomes with Early versus Delayed Second-Line Chemotherapy for Patients with Relapsed Ovarian Cancer



No difference in overall survival between early and delayed second-line chemotherapy

"It is very clear from this study that in the early treatment arm, based on a rising CA125, second-line chemotherapy started a median of 4.8 months earlier than in the delayed arm. Third-line chemotherapy also started a median of 4.6 months earlier than in the delayed arm. Despite this, the early treatment did not improve survival, with a hazard ratio of 1.00, and early chemotherapy does not improve quality of life; in fact, it actually makes it worse.

So, how does this impact on our clinical practice? For the first time women can be reassured that there is no benefit from early detection of relapse by routine CA125 measurements. Even if the CA125 rises, chemotherapy can be delayed until signs or symptoms of tumor recurrence."

SOURCE: With permission from Rustin GJ et al. *Proc ASCO* 2009;**Abstract 1**.

Track 9

DR LOVE: Would you discuss the CALYPSO study and what you think it means for clinical practice?

DR PENSON: This trial compared pegylated liposomal doxorubicin (PLD)/carboplatin to paclitaxel/carboplatin for platinum-sensitive recurrent ovarian cancer. It not only showed equivalence in terms of clinical benefit but also a progression-free survival advantage (Pujade-Lauraine 2009), which is extraordinary. Patients fared better on PLD/carboplatin than on paclitaxel/carboplatin for their recurrent disease. From my perspective, this was a "big splash" study, and I immediately switched to using PLD as second-line therapy for platinum-sensitive disease and have administered it to a number of patients.

DR LOVE: What was reported in terms of side effects and toxicity, and what was your experience?

DR PENSON: The curious effect reported was dramatically fewer allergic reactions to carboplatin in the PLD/carboplatin arm — five percent versus 18 percent. The other toxicity issues appeared to be favorable with PLD/carboplatin compared to paclitaxel/carboplatin — potentially no alopecia, seven percent versus 84 percent, significantly less neurotoxicity — four percent versus 27 percent — and everyone anticipating a better quality of life.

The hematologic toxicity was considerable, and my clinical experience is that a great deal of thrombocytopenia and neutropenia occurs. However, not losing your hair and having less neurotoxicity is a major advantage. ■

SELECT PUBLICATIONS

Azad NS et al. **Combination targeted therapy with sorafenib and bevacizumab results in enhanced toxicity and antitumor activity.** *J Clin Oncol* 2008;26(22):3709-14.

Matulonis UA et al. **Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer.** *J Clin Oncol* 2009;27(33):5601-6.

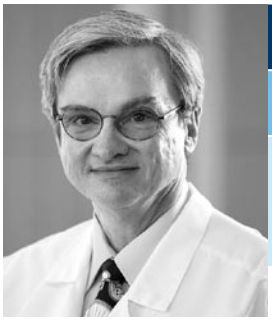
Pignata S et al. **Carboplatin and pegylated liposomal doxorubicin for advanced ovarian cancer: Preliminary activity results of the MITO-2 phase III trial.** *Oncology* 2009a;76(1):49-54.

Pignata S et al. **Pegylated liposomal doxorubicin combined with carboplatin: A rational treatment choice for advanced ovarian cancer.** *Crit Rev Oncol Hematol* 2009b;[Epub ahead of print].

Power P et al. **Efficacy of pegylated liposomal doxorubicin (PLD) plus carboplatin in ovarian cancer patients who recur within six to twelve months: A phase II study.** *Gynecol Oncol* 2009;114(3):410-4.

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**.

Rustin GJ et al. **A randomized trial in ovarian cancer (OC) of early treatment of relapse based on CA125 level alone versus delayed treatment based on conventional clinical indicators (MRC OV05/EORTC 55955 trials).** *Proc ASCO* 2009;**Abstract 1**.



INTERVIEW

Robert J Morgan, MD

Dr Morgan is Director of Continuing Medical Education and Co-Director of the Gynecologic and Peritoneal Malignancy Program at City of Hope in Duarte, California.

Tracks 1-12

Track 1 Perspective on MRC OV05/EORTC-55955: Treatment based on CA125 level versus conventional clinical indicators

Track 2 Perspective on the CALYPSO trial and clinical experience with liposomal doxorubicin for the treatment of ovarian cancer

Track 3 **Case discussion:** A 74-year-old woman with peritoneal carcinomatosis from papillary serous ovarian cancer enrolls in SWOG-S0009 and undergoes optimal cytoreduction with interval debulking surgery after neoadjuvant carboplatin/paclitaxel

Track 4 Long-term disease control of relapsed ovarian cancer with sequential chemotherapy and endocrine therapy

Track 5 Metronomic oral cyclophosphamide and bevacizumab for relapsed platinum-resistant ovarian cancer

Track 6 **Case discussion:** A 57-year-old woman whose cancer was initially suboptimally debulked presents with diffuse carcinomatosis and recurrent clinically symptomatic ascites

Track 7 Activity of the pan-VEGFR TKI cediranib in recurrent ovarian cancer

Track 8 Intraperitoneal bevacizumab for palliation of ascites in refractory ovarian cancer

Track 9 GOG-0218: Carboplatin/paclitaxel with or without bevacizumab, with or without extended bevacizumab for newly diagnosed, suboptimally debulked advanced ovarian cancer

Track 10 Clinical use of intraperitoneal cisplatin/paclitaxel for ovarian cancer

Track 11 Counseling patients about the side effects of intraperitoneal chemotherapy

Track 12 Perspective on the evolution of the NCCN practice guidelines in ovarian cancer

Select Excerpts from the Interview

Track 2

DR LOVE: What are your thoughts on the clinical implications of the CALYPSO trial data that were recently presented (2.1)?

DR MORGAN: I believe that we have to wait for published survival data before we can consider substituting a carboplatin/pegylated liposomal doxorubicin (PLD) regimen for a carboplatin/paclitaxel combination except for select

individuals — for example, for patients who may have preexisting peripheral neuropathy or patients who are predisposed to peripheral neuropathy, such as those with diabetes.

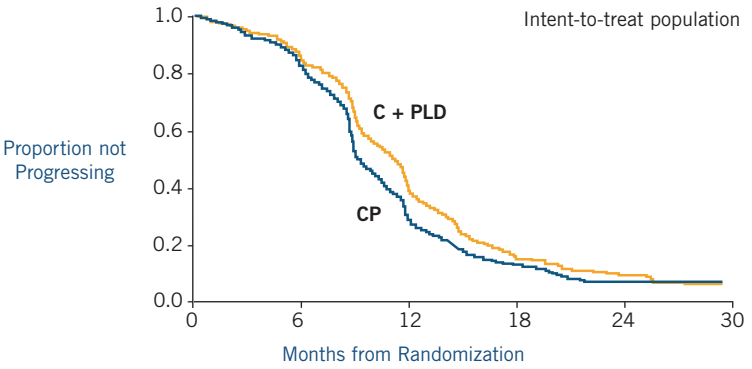
The major trial published recently that addressed this issue was the GOG trial in which patients were randomly assigned to receive paclitaxel/carboplatin versus four investigational regimens. These regimens included various schedules of gemcitabine and PLD.

All five combinations had identical survival curves with different toxicity profiles, and the overall conclusion was that paclitaxel/carboplatin remained the backbone of standard chemotherapy for ovarian cancer (Bookman 2009). However, an additional conclusion that can be drawn is that other combinations can be used for various reasons, depending on the patient. I use PLD frequently for ovarian cancer for several reasons. First, it only has to be administered every three to four weeks, and other second-line therapies are administered weekly.

In addition, the toxicity profile is tolerable. Patients may experience some hand-foot syndrome and mucositis. However, minimal hematologic toxicity is involved and patients experience little nausea and vomiting. Patients also appreciate the fact that they don't lose their hair from this agent. So I use it frequently, although not at the 50-mg/m^2 monotherapy dose. Most people reduce the initial monotherapy dose to 40 mg/m^2 because of the cutaneous toxicity. The dose can be raised from there if patients tolerate it well.

2.1

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



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

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

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

Tracks 8, 10-11

DR LOVE: Would you discuss the issue of intraperitoneal chemotherapy for patients with ovarian cancer?

DR MORGAN: The debate regarding intraperitoneal chemotherapy versus intravenous chemotherapy for ovarian cancer is constant. I'm an advocate of intraperitoneal therapy on the basis of the published data. The finding of an approximate 16-month survival improvement in the Armstrong trial reported several years ago is compelling (Armstrong 2006).

The concern with intraperitoneal chemotherapy is that the major regimen shown to have a benefit was the Armstrong regimen, which involves dose-aggressive and dose-intensive cisplatin. Due to the severe toxicity — primarily nausea, vomiting and myelosuppression — doctors have been unable to accept this regimen. Intraperitoneal chemotherapy must be administered where the physicians and the nurses are familiar with the administration of the drug as well as the use of appropriate supportive care medications. It takes specialized knowledge to administer it safely, but I have even administered it to a number of patients in their seventies who have tolerated it well.

DR LOVE: How do you counsel patients with regard to the side effects and toxicity associated with intraperitoneal versus intravenous chemotherapy?

DR MORGAN: I caution patients that intraperitoneal chemotherapy is much more intensive and requires a greater investment in time and effort from the patient. Initially, my experiences using the Armstrong day one, day two regimen on an outpatient basis were not good. I admitted patients for symptom control and hydration because of the high-dose cisplatin. Subsequently, with more experience, my nurse practitioner and I observed a delayed toxicity associated with the cisplatin. However, patients are tolerating it much better if they have home healthcare services or if they come back to the clinic daily for about a week after chemotherapy to receive intravenous hydration.

DR LOVE: How has the issue of intraperitoneal chemotherapy played out in the NCCN guidelines process as you have observed it as the chair of the ovarian cancer practice guidelines committee? I know that a Phase III Gynecologic Oncology Group study is currently evaluating bevacizumab with intravenous versus intraperitoneal chemotherapy (2.2).

DR MORGAN: Early on we had considerable discussion about the role of intraperitoneal chemotherapy. In fact, in the initial NCCN guidelines, intraperitoneal chemotherapy was considered a Category 3 recommendation, meaning that major disagreements about its role existed between institutions. Some institutions considered it an option whereas others considered it to be essentially malpractice. Data have accumulated over the years — initially from the Alberts study (Alberts 1996) and subsequently from the Markman and Armstrong studies (Markman 2001; Armstrong 2006) — and we now consider intraperitoneal chemotherapy to be a Category 1 recommendation. ■

2.2 A Phase III Clinical Trial of Bevacizumab with Intravenous or Intraperitoneal Chemotherapy

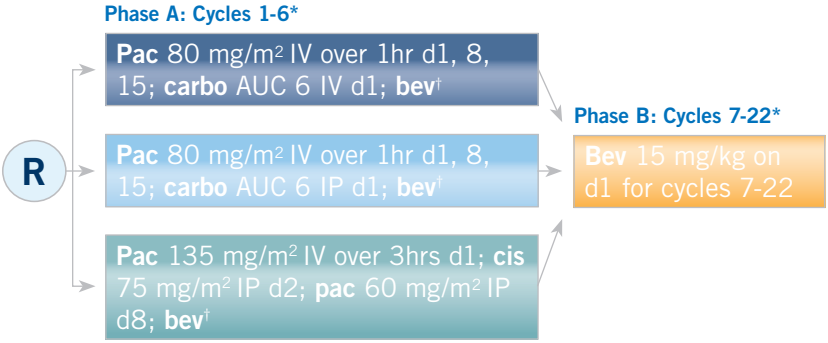
Protocol IDs: GOG-0252, NCT00951496

Target Accrual: 1,250

Eligibility

- Stage II, III or IV ovarian epithelial, fallopian tube or primary peritoneal carcinoma with either optimal (≤1-cm residual disease) or suboptimal residual disease
- Surgery for diagnosis, staging and/or cytoreduction within the past 12 weeks (No residual disease > 1 cm)
- No history or evidence of primary brain tumor or brain metastases
- No metastatic tumor in the parenchyma of the liver or lungs with proximity to large vessels

Pac = paclitaxel; carbo = carboplatin; bev = bevacizumab; cis = cisplatin



* Continue regimen every three weeks for six cycles of chemotherapy and a total of 22 cycles including bev unless toxicity or disease progression intervenes

† 15 mg/kg IV on d1 beginning on cycle 2

SOURCE: **www.clinicaltrials.gov**, December 28, 2009.

SELECT PUBLICATIONS

Alberts DS et al. **Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer.** N *Engl J Med* 1996;335(26):1950-5.

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

Bookman MA et al. **Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: A Phase III trial of the Gynecologic Cancer Intergroup.** *J Clin Oncol* 2009;27(9):1419-25.

Markman M et al. **Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: An intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group.** *J Clin Oncol* 2001;19(4):1001-7.

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

INTERVIEW

Don S Dizon, MD

Dr Dizon is Assistant Professor of Obstetrics-Gynecology and Medicine at the Warren Alpert Medical School of Brown University, Director of Medical Oncology and Integrative Care and Co-Director at the Center for Sexuality, Intimacy and Fertility at the Women and Infant's Program in Women's Oncology in Providence, Rhode Island.

Tracks 1-14

Track 1 Benefit from surgical staging of apparent early ovarian cancer in patients receiving chemotherapy

Track 2 HER3 expression as a predictor of response to pertuzumab in ovarian cancer

Track 3 **Case discussion:** A 43-year-old woman who presents with abdominal pain, bloating and a CA125 level of 2,000 U/mL undergoes optimal resection of a Stage IIIC ovarian tumor

Track 4 Adjuvant intraperitoneal therapy for patients with optimally resected ovarian cancer

Track 5 Potential side effects of intraperitoneal therapy

Track 6 Ongoing adjuvant clinical trials of chemotherapy and biologic therapy for ovarian cancer

Track 7 Activity of bevacizumab monotherapy in ovarian cancer

Track 8 Bevacizumab-associated bowel perforations in ovarian cancer

Track 9 Clinical use of bevacizumab off protocol for patients with relapsed ovarian cancer and refractory ascites

Track 10 **Case discussion:** A 45-year-old woman treated for Stage IIIC ovarian cancer has an increase in CA125 after 13 months with negative CT findings and presents nine months later with biopsy-confirmed abdominal metastases

Track 11 Treatment considerations for patients with recurrent platinum-sensitive ovarian cancer

Track 12 Liposomal doxorubicin for recurrent ovarian cancer

Track 13 **Case discussion:** A 68-year-old woman with heavily treated relapsed ovarian cancer experiences a dramatic improvement of symptomatic, disabling ascites during 14 months of bevacizumab monotherapy

Track 14 Clinical applications of hormonal therapy in ovarian cancer

Select Excerpts from the Interview

Track 2

DR LOVE: What do we know about pertuzumab and its potential role in treating ovarian cancer?

DR DIZON: Pertuzumab is a HER dimerization inhibitor. As opposed to trastuzumab, which blocks HER2 itself and the downstream pathways from

HER2, pertuzumab blocks HER2 from associating or dimerizing with other members of its receptor family — most importantly with HER3. Pertuzumab does not require HER2 overexpression in order to be effective.

In clinical trials for women with previously treated platinum-resistant ovarian cancer, the suggestion is that women whose tumors had low HER3 mRNA levels not only had poor prognoses on chemotherapy but also may have received greater benefits from treatment with pertuzumab and gemcitabine in combination (Amler 2008; [3.1]). So as HER2 overexpression is a marker in breast cancer, low HER3 mRNA levels may be the marker of activity for pertuzumab in ovarian cancer.

The hypothesis right now is that HER3 may be overactive on the cell surface, leading to negative feedback at the level of mRNA. Pertuzumab may be the first agent beyond breast oncology or chronic myeloid leukemia with which we can target a specific patient population who experience relapse and fulfill the mission of individualizing and tailoring anticancer treatment.

3.1

HER Pathway Gene Expression Analysis in a Phase II Study of Pertuzumab (P) and Gemcitabine (G) versus G and Placebo for Patients with Platinum-Resistant Epithelial Ovarian Cancer (CDDP-R EOC)

Efficacy	G and P	G and placebo	Hazard ratio (95% CI)
Median PFS (months)			
All patients (n = 130)	2.9	2.6	0.66* (0.43-1.03)
Low HER3 (n = 61)	5.3	1.4	0.34 (0.18-0.63)
High HER3 (n = 61)	2.8	5.5	1.48 (0.83-2.63)
Median OS (months)			
All patients (n = 130)	13.0	13.1	0.91* (0.58-1.41)
Low HER3 (n = 61)	11.8	8.4	0.62 (0.35-1.11)
High HER3 (n = 61)	16.1	18.2	1.59 (0.80-3.20)

* All patient analyses were stratified by ECOG status, disease measurability and prior number of regimens for CDDP-R disease.

"This exploratory analysis suggests that low tumor HER3 gene expression levels may be prognostic in patients with CDDP-R EOC. Pertuzumab treatment may add to gemcitabine's clinical activity in patients whose tumors have low HER3 gene expression. These data suggest that HER3 mRNA expression levels may be a potential prognostic and predictive diagnostic biomarker."

SOURCE: Amler L et al. *Proc ASCO* 2008;**Abstract 5552**.

Track 6

DR LOVE: What are some of the ongoing clinical trials and trials not yet reported that are evaluating the role of biologic agents?

DR DIZON: Many centers are conducting adjuvant trials in ovarian cancer incorporating biologic agents. One of the trials I was involved with was a Phase II trial of carboplatin/paclitaxel with bevacizumab as first-line treat-

ment and consolidation for advanced ovarian cancer. The manuscript has been submitted for publication, and the three-year progression-free survival is 58 percent in our study of 62 patients (Penson 2009).

GOG-0218 is a randomized trial evaluating the addition of bevacizumab to a carboplatin/paclitaxel backbone (3.2). A series of Phase I GOG trials is evaluating intraperitoneal approaches, some of which will include biologic therapy and anti-angiogenic treatment.

3.2

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

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 mg/mL x min) every 21 days x 6 cycles

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

SOURCE: NCI Physician Data Query, December 2009.

Track 7

DR LOVE: Would you review the available clinical trial data and translational work on bevacizumab in ovarian cancer?

DR DIZON: Bevacizumab is being explored in every possible setting in ovarian cancer. The GOG-170D study evaluating single-agent bevacizumab for women with relapsed ovarian cancer who had received two prior therapies demonstrated exciting results.

The primary endpoint was prolongation of progression-free survival at six months — and that was in approximately 40 percent of patients. Of more interest was the fact that we found responders to an anti-angiogenic drug in ovarian cancer among women who had received prior therapies. We

reported an approximate 20 percent response rate (Burger 2007; [3.3]). The toxicity reported was mild and manageable. High blood pressure was an issue, however.

DR LOVE: Another interesting facet is the effect of anti-VEGF therapy on ascites.

DR DIZON: It is fascinating. I've seen women bed bound from refractory ascites recover their lives with bevacizumab. We might be oversimplifying the effects of bevacizumab. We consider it an anti-VEGF agent, but additional effects may still be characterized. ■

3.3

GOG-170D: 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%
Median duration of response	10.3 months
Stable disease	51.6%
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.

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.** *Proc ASCO* 2008;**Abstract 5552**.

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.

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**.

Penson RT et al. **Phase II study of carboplatin, paclitaxel and bevacizumab with maintenance bevacizumab as first-line chemotherapy for advanced müllerian tumors.** *J Clin Oncol* 2009;[Epub ahead of print].

INTERVIEW

Robert S Mannel, MD

Dr Mannel is Director at OU Cancer Institute, Professor and Chairman in the Department of Obstetrics and Gynecology and The Rainbolt Family Chair in Cancer at The University of Oklahoma College of Medicine in Oklahoma City, Oklahoma.

Tracks 1-13

Track 1 **Case discussion:** A 46-year-old woman with a Grade III serous adenocarcinoma of the ovary undergoes total abdominal hysterectomy and bilateral salpingo-oophorectomy with no other staging procedures performed

Track 2 Rationale for a surgical staging procedure for patients with incompletely staged disease

Track 3 Adjuvant chemotherapy for patients with and without completely surgically staged early ovarian cancer

Track 4 Active clinical investigations in early-stage ovarian cancer

Track 5 Intraperitoneal administration of chemotherapy for optimally debulked ovarian cancer

Track 6 **Case discussion:** A 75-year-old woman with extensive ovarian cancer undergoes a bilateral oophorectomy, omentectomy, radical intraperitoneal debulking and sigmoid colon resection with low rectal anastomosis and has no visible residual disease

Track 7 Activity of bevacizumab in persistent or recurrent, platinum-resistant ovarian cancer

Track 8 Tolerability of adjuvant chemotherapy for elderly patients with ovarian cancer

Track 9 Potential mechanisms of action of bevacizumab in ovarian cancer

Track 10 Off-protocol use of bevacizumab for recurrent ovarian cancer

Track 11 Treatment algorithm for recurrent ovarian cancer

Track 12 Tolerability and convenience of liposomal doxorubicin for recurrent platinum-resistant ovarian cancer

Track 13 Maintenance therapy for ovarian cancer

Select Excerpts from the Interview

Tracks 6, 8

Case discussion

A 75-year-old woman with extensive ovarian cancer undergoes a bilateral oophorectomy, omentectomy, radical intraperitoneal debulking and sigmoid colon resection with low rectal anastomosis and has no visible residual disease

DR MANNEL: The studies clearly confirm that a patient's long-term outcome is based, to a large extent, on what the surgery allows you to accomplish.

Dennis Chi from Memorial Sloan-Kettering and others have reported on the effect of residual disease with outcome (Chi 2006). The consensus in the literature indicates that the smaller the residual disease, the better the outcome. Ideally, we strive for no residual disease. That seems to be the big break point, and we were able to accomplish that with this patient.

Now, having achieved that, we know that with appropriately aggressive chemotherapy, her survival should be quite good. The median survival in GOG-0172 for patients who received intraperitoneal therapy was 67 months, and those patients could have up to one centimeter of residual disease (Armstrong 2006).

That trial has now been followed for nine years, and we still have not reached median survival for patients with Stage III ovarian cancer whose disease was debulked to no residual disease — which is phenomenal.

This particular patient participated in a registry trial evaluating bevacizumab in combination with intraperitoneal chemotherapy (NCT00511992; [4.1]). We used the GOG-0172 backbone of intraperitoneal cisplatin and intravenous paclitaxel.

Bevacizumab is administered every three weeks and is then continued as maintenance therapy after six cycles of the chemotherapy/bevacizumab. We have not reported our findings yet, but we have not seen any excess toxicity and the regimen appears to be feasible.

4.1

Phase II Study of Paclitaxel, Intraperitoneal (IP) Cisplatin and IV Bevacizumab Followed by Bevacizumab Consolidation for Advanced Ovarian and Peritoneal Carcinoma

Protocol ID: NCT00511992
Target Accrual: 20

Eligibility

Stage II/III epithelial ovarian cancer, primary peritoneal carcinoma or ovarian carcinosarcoma, excluding patients with Stage IV disease or suboptimally debulked disease after primary cytoreductive surgery

Initial treatment

Paclitaxel 135 mg/m^2 IV day 1 every 21 days x 6 cycles

Cisplatin 75 mg/m^2 IP day 2 every 21 days x 6 cycles

Bevacizumab 15 mg/kg day 1 (beginning cycle 2) every 21 days x 5 cycles

Consolidation treatment

Bevacizumab 15 mg/kg every 21 days x 12 cycles

SOURCE: **www.clinicaltrials.gov**. Accessed December 2009.

Tracks 7, 9

DR LOVE: What's your perspective on how bevacizumab works and whether it works differently in different tumors?

DR MANNEL: In our Phase II GOG-170D trial of bevacizumab monotherapy for recurrent ovarian cancer, we observed absolutely incredible results (Burger 2007; [3.3, page 14]). The response rate was approximately 20 percent, with a six-month progression-free survival rate of approximately 40 percent. This is in a platinum-pretreated patient population, half of whom were platinum-resistant.

You would not expect those results, even with our best cytotoxic agents. So, in a Phase II setting, bevacizumab could be considered the most effective agent we've seen, and it has been moved into our current, large placebo-controlled trial in the up-front setting (3.2, page 13).

In terms of how it works, it was initially believed that bevacizumab inhibited neovascularization and affected the blood supply to the tumor. Subsequently, questions have arisen about whether it changes permeability of blood vessels and inhibits metastatic disease. Others have speculated that it may have direct antitumor effects on cancer cells. I'm probably similar to a lot of clinical researchers — I know it works, but I can't tell you how.

A fair amount of literature supports the role of VEGF inhibitors in controlling ascites. The mechanism of action in that instance may have more to do with affecting the cytokine milieu in ovarian cancer. I believe that bevacizumab and other VEGF inhibitors probably act at a variety of different levels, and in ovarian cancer it may have a greater effect because of its effect on the cytokine matrix.

Tracks 11-12

DR LOVE: What is your algorithm for selecting sequential agents for patients with platinum-refractory recurrent disease?

DR MANNEL: These patients should be offered clinical trials because they do not fare well with any agent. Off trial, PLD is probably our first-line choice. It is administered monthly, it is fairly nontoxic and well tolerated and alopecia is not an issue. If patients experience palmar rash, the dose can be reduced. Cardiotoxicity does not seem to be an issue as with doxorubicin. I've seen patients fare well with 16 or 18 treatment cycles up to a couple of years. ■

SELECT PUBLICATIONS

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

Burger RA et al. **Phase 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.

Chi DS et al. **What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)?** *Gynecol Oncol* 2006;103(2):559-64.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The OCEANS study is evaluating gemcitabine and carboplatin with or without _____ for patients with platinum or potentially platinum-sensitive recurrent disease.**
   a. Bevacizumab
   b. Cediranib
   c. Olaparib

2. **The MRC OV05/EORTC-55955 randomized trial in relapsed ovarian cancer of early treatment based on CA125 level alone versus delayed treatment based on conventional clinical indicators reported a statistically significant overall survival improvement for patients receiving early second-line chemotherapy.**
   a. True
   b. False

3. **The CALYPSO trial reported a progression-free survival improvement of approximately _____ for patients with relapsed platinum-sensitive ovarian cancer treated with carboplatin and PLD compared to carboplatin and paclitaxel.**
   a. Two months
   b. Four months
   c. Six months

4. **A five-arm Phase III GOG trial evaluating paclitaxel/carboplatin versus different schedules of gemcitabine and PLD for advanced-stage ovarian cancer reported a statistically significant overall survival improvement for patients treated with gemcitabine and PLD.**
   a. True
   b. False

5. **Armstrong and colleagues reported significantly improved _____ for patients with newly diagnosed, optimally debulked Stage III ovarian cancer treated with an intensive regimen of intravenous paclitaxel followed by intraperitoneal cisplatin and paclitaxel compared to intravenous paclitaxel with cisplatin therapy alone.**
   a. Overall survival
   b. Progression-free survival
   c. Both of the above
   d. None of the above

6. **Exploratory analysis by Amler and colleagues suggests that pertuzumab may add to the clinical activity of gemcitabine in patients whose tumors have ____ HER3 gene expression.**
   a. Low
   b. High

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

8. **In a Phase II trial (GOG-170D) for patients with persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer, bevacizumab monotherapy resulted in a response rate of approximately _____.**
   a. Seven percent
   b. 21 percent
   c. 40 percent

9. **A randomized Phase III study evaluating three versus six cycles of adjuvant carboplatin and paclitaxel for patients with early-stage epithelial ovarian cancer reported _____ toxicity with the six-cycle regimen.**
   a. Decreased
   b. Equivalent
   c. Increased

10. **The Phase III GOG-178 trial reported a statistically significant improvement in _____ with 12 versus three monthly cycles of paclitaxel administered to patients with advanced ovarian cancer.**
    a. Progression-free survival
    b. Overall survival
    c. Both of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Ovarian Cancer Update — Issue 1, 2009

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
Role of surgical staging in early ovarian cancer	4 3 2 1	4 3 2 1
MRC OV05/EORTC-55955: Early treatment based on CA125 level alone versus delayed treatment based on conventional clinical indicators in relapsed ovarian cancer	4 3 2 1	4 3 2 1
Utility of bevacizumab for palliation of ascites	4 3 2 1	4 3 2 1
GOG-0218: Carboplatin/paclitaxel with or without bevacizumab and with or without extended bevacizumab for newly diagnosed, suboptimally debulked advanced ovarian cancer	4 3 2 1	4 3 2 1
CALYPSO: Carboplatin/PLD versus carboplatin/paclitaxel for relapsed platinum-sensitive 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:

- Consider the utility of evaluating CA125 serum levels in patients with ovarian cancer in a state of remission..... 4 3 2 1 N/M N/A
- Evaluate the investigation of biomarkers for prediction of response to biologic agents for the treatment of 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 in ovarian cancer, and identify patients who may benefit from this therapeutic approach ..... 4 3 2 1 N/M N/A
- Consider the pros and cons of immediate adjuvant chemotherapy versus surgical staging followed by adjuvant chemotherapy when developing a treatment algorithm for patients with early incompletely staged 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 faculty and editor for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Richard T Penson, MD, MRCP	4 3 2 1	4 3 2 1
Robert J Morgan, MD	4 3 2 1	4 3 2 1
Don S Dizon, MD	4 3 2 1	4 3 2 1
Robert S Mannel, 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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