

# DATA AND PERSPECTIVES

## Clinical Investigators Review Key Research Developments and Current Cases in Gynecologic Oncology

### CME Information

#### TARGET AUDIENCE

This activity is intended for gynecologic oncologists and other healthcare providers involved in the treatment of ovarian, cervical and endometrial cancer.

#### OVERVIEW OF ACTIVITY

In 2014 it is anticipated that approximately 94,990 new cases of gynecologic cancer — which includes cancer of the ovaries, uterine corpus (endometrial cancer), uterine cervix (cervical cancer), vulva and vagina — will be documented in the United States and 28,790 individuals will succumb to these diseases. As with many other tumors, patient outcomes are critically dependent on effective multidisciplinary care. Despite many commonalities, each of these diseases is in fact quite distinct, and in this regard management algorithms employed for each are varied.

Existing and emerging multimodality treatment regimens used in the routine management of these diseases necessitate the physician's working knowledge of novel surgical, radiation and systemic therapeutic techniques. Ongoing clinical trials will continue to refine the optimal management of these tumors, and the introduction of innovative, targeted compounds may offer individualized treatment options that provide increased efficacy and improved tolerability. In order to offer optimal patient care — including the option of clinical trial participation — clinicians who care for patients with gynecologic cancers must be well informed of these advances. By providing information on the latest research developments and their potential application to routine practice, this activity is designed to assist gynecologic oncologists and other healthcare providers with the formulation of up-to-date clinical management strategies for various gynecologic cancers.

#### LEARNING OBJECTIVES

- Employ current clinical guidelines and available data in the selection of treatment options for patients with commonly diagnosed gynecologic cancers.
- Apply the results of emerging research with angiogenesis inhibition to the development of therapeutic strategies for patients with advanced epithelial ovarian cancer.

- Summarize available research data on the activity of PARP inhibitors in patients with advanced ovarian cancer with or without BRCA mutations.
- Appreciate emerging clinical trial data documenting the benefit of anti-angiogenic therapy in combination with chemotherapy for patients with metastatic, recurrent or persistent cervical cancer, and consider this information in treatment decision-making.
- Develop an understanding of the emerging efficacy data and toxicity profiles of investigational agents in common gynecologic cancers to effectively prioritize clinical trial opportunities for appropriate patients.

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reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

**FACULTY** — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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**Hardware/Software Requirements:**

A high-speed Internet connection  
A monitor set to 1280 x 1024 pixels or more  
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later  
Adobe Flash Player 10.2 plug-in or later  
Adobe Acrobat Reader  
(Optional) Sound card and speakers for audio

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## Select Publications

### Bradley J Monk, MD

**A randomized Phase III trial of cisplatin plus paclitaxel with and without NCI-supplied bevacizumab (NSC #704865, IND #113912) versus the non-platinum doublet, topotecan plus paclitaxel, with and without NCI-supplied bevacizumab, in stage IVB, recurrent or persistent carcinoma of the cervix. NCT00803062**

Aghajanian C et al. **OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer.** *J Clin Oncol* 2012;30(17):2039-45.

Augustin HG et al. **Control of vascular morphogenesis and homeostasis through the angiopoietin-Tie system.** *Nat Rev Mol Cell Biol* 2009;10(3):165-77.

Burger RA et al; Gynecologic Oncology Group. **Incorporation of bevacizumab in the primary treatment of ovarian cancer.** *N Engl J Med* 2011;365(26):2473-83.

Du Bois A et al. **Randomized, double-blind, phase III trial of pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC): Results of an international Intergroup trial (AGO-OVAR16).** *Proc ASCO* 2013;Abstract LBA5503.

Du Bois A et al. **Addition of epirubicin as a third drug to carboplatin-paclitaxel in first-line treatment of advanced ovarian cancer: A prospectively randomized gynecologic cancer intergroup trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens.** *J Clin Oncol* 2006;24(7):1127-35.

Falcón BL et al. **Contrasting actions of selective inhibitors of angiopoietin-1 and angiopoietin-2 on the normalization of tumor blood vessels.** *Am J Pathol* 2009;175(5):2159-70.

Ledermann JA et al. **Randomised double-blind phase III trial of cediranib (AZD 2171) in relapsed platinum sensitive ovarian cancer: Results of the ICON6 trial.** *Proc ESMO-ECCO* 2013;Abstract LBA10.

Monk BJ et al. **A phase III, randomized, double-blind trial of weekly paclitaxel plus the angiopoietin 1 and 2 inhibitor, trebananib, or placebo in women with recurrent ovarian cancer: TRINOVA-1.** *Proc ESMO-ECCO* 2013;Abstract 41.

Monk BJ et al. **Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study.** *J Clin Oncol* 2009;27(7):1069-74.

Ostör AG. **Natural history of cervical intraepithelial neoplasia: A critical review.** *Int J Gynecol Pathol* 1993;12(2):186-92.

Perren TJ et al; ICON7 Investigators. **A phase 3 trial of bevacizumab in ovarian cancer.** *N Engl J Med* 2011;365(26):2484-96.

Podar K, Anderson KC. **The pathophysiologic role of VEGF in hematologic malignancies: Therapeutic implications.** *Blood* 2005;105(4):1383-95.

Poon RT et al. **Clinical implications of circulating angiogenic factors in cancer patients.** *J Clin Oncol* 2001;19(4):1207-25.

Pujade-Lauraine E et al. **AURELIA: A randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC).** *Proc ASCO* 2012;Abstract LBA5002.

Sallinen H et al. **Preoperative angiopoietin-2 serum levels: A marker of malignant potential in ovarian neoplasms and poor prognosis in epithelial ovarian cancer.** *Int J Gynecol Cancer* 2010;20(9):1498-505.

Scharpfenecker M et al. **The Tie-2 ligand angiopoietin-2 destabilizes quiescent endothelium through an internal autocrine loop mechanism.** *J Cell Sci* 2005;118(Pt 4):771-80.

Schiffman M, Kjaer SK. **Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia.** *J Int Cancer Natl Monogr* 2003;31:14-9.

Tewari KS et al. **Improved survival with bevacizumab in advanced cervical cancer.** *N Engl J Med* 2014;370(8):734-43.

Tewari KS et al. **Incorporation of bevacizumab in the treatment of recurrent and metastatic cervical cancer: A phase III randomized trial of the Gynecologic Oncology Group.** *Proc ASCO* 2013;Abstract 03.

Tewari KS et al. **Development and assessment of a general theory of cervical carcinogenesis utilizing a severe combined immunodeficiency murine-human xenograft model.** *Gynecol Oncol* 2000;77(1):137-48.

Yost KJ, Eton DT. **Combining distribution- and anchor-based approaches to determine minimally important differences: The FACIT experience.** *Eval Health Prof* 2005;28(2):172-91.

### **Ursula A Matulonis, MD**

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

Bell D et al. **Integrated genomic analyses of ovarian carcinoma.** *Nature* 2011;474(7353):609-15.

**Cediranib maleate and olaparib in treating patients with recurrent ovarian, fallopian tube, peritoneal cancer, or triple-negative breast cancer. NCT01116648**

Hammond E et al. **Hypoxia links ATR and p53 through replication arrest.** *Mol Cell Biol* 2002;22(6):1834-43.

Ledermann J et al. **Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (SOC) and a BRCA mutation (BRCAm).** *Proc ASCO* 2013;Abstract 5505.

Ledermann J et al. **Randomised double-blind phase III trial of cediranib (AZD 2171) in relapsed platinum sensitive ovarian cancer: Results of the ICON6 trial.** *Proc ESMO* 2013;Abstract 10.

Ledermann J et al. **Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.** *N Engl J Med* 2012;366(15):1382-92.

Liu J et al. **PARP inhibitors in ovarian cancer: Current status and future promise.** *Gynecol Oncol* 2014;133(2):362-9.

Liu J et al. **A Phase 1 trial of the poly(ADP-ribose) polymerase inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cediranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer.** *Eur J Cancer* 2013;49(14):2972-8.

Olcina M et al. **Targeting hypoxic cells through the DNA damage response.** *Clin Cancer Res* 2010;16(23):5624-9.

### **Don S Dizon, MD**

Cancer Genome Atlas Research Network. **Integrated genomic characterization of endometrial carcinoma.** *Nature* 2013;497(7447):67-73.

Ojesina A et al. **Landscape of genomic alterations in cervical carcinomas.** *Nature* 2014;506(7488):371-5.

Verhaak R et al. **Prognostically relevant gene signatures of high-grade serous ovarian carcinoma.** *J Clin Invest* 2013;123(1):517-25.

### **Robert A Burger, MD**

Chan JK et al. **Rapidly recurrent small cell neuroendocrine carcinoma of the uterine cervix presenting with syndrome of inappropriate antidiuretic hormone secretion (SIADH).** *Proc ESGO* 2013.

Katsumata N et al. **Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: A phase 3, open-label, randomised controlled trial.** *Lancet* 2009;374(9698):1331-8.

Kehoe S et al. **Chemotherapy or upfront surgery for newly diagnosed advanced ovarian cancer: Results from the MRC CHORUS trial.** *Proc ASCO* 2013;Abstract 5500.

Vergote I et al. **Neoadjuvant chemotherapy or primary surgery in Stage IIIC or IV ovarian cancer.** *N Engl J Med* 2010;363(10):943-53.

Xiong X et al. **Cell cycle dependent antagonistic interactions between paclitaxel and carboplatin in combination therapy.** *Cancer Biol Ther* 2007;6(7):1067-73.