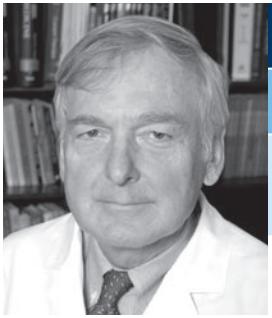

INTERVIEW

Robert F Ozols, MD, PhD

Dr Ozols is Chief Clinical Officer, Emeritus at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

Tracks 1-13

Track 1 **Case discussion:** A 70-year-old woman with optimally debulked OC experiences disease relapse after receiving maintenance bevacizumab on the GOG-0218 study

Track 2 Incorporation of up-front bevacizumab into the management of OC

Track 3 Relevance of progression-free survival as an endpoint in OC

Track 4 Evolving role of bevacizumab in the initial management of OC

Track 5 Targeting PARP in patients with germline BRCA mutations

Track 6 Concept of BRCAness in patients with the wild-type BRCA gene

Track 7 **Case discussion:** A 65-year-old woman with relapsed OC and known BRCA mutation receives single-agent olaparib in a Phase II study

Track 8 **Case discussion:** A 60-year-old woman with optimally debulked OC develops recurrent disease six months after IP cisplatin/paclitaxel and receives carboplatin/gemcitabine

Track 9 Investigating IV bevacizumab with IP chemotherapy in optimally debulked OC

Track 10 Targeting the folate receptor with the humanized monoclonal antibody farletuzumab in OC

Track 11 Current status of pertuzumab in HER2-positive OC

Track 12 Moving toward personalized treatment of relapsed platinum-sensitive OC

Track 13 Weekly versus three-weekly paclitaxel in OC

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: What are your thoughts on the results of the GOG-0218 study (Burger 2010; [3.1, 3.2, 3.3])?

DR OZOLS: I certainly would lean toward using chemotherapy/bevacizumab followed by maintenance bevacizumab, as I agree that a four-month improvement in PFS is a benefit. Some toxicity occurs and patients have to be aware of that, but overall I believe it is certainly a reasonable approach.

Because oncologists are familiar with using bevacizumab in other tumor types, they are not going to be afraid to administer it in this setting. Hypertension is manageable, and quality of life is good. Hopefully, we will obtain

more data from the GOG-0218 trial and additional ongoing studies. Some of these studies, such as ICON7, are also evaluating bevacizumab for earlier-stage ovarian cancer. If these additional studies are positive, they will add to the database indicating that we can incorporate bevacizumab into the front-line management of ovarian cancer.

Tracks 5-6

DR LOVE: Where are we currently in research on PARP inhibitors in ovarian cancer?

DR OZOLS: The development of PARP inhibitors has been an exciting area in ovarian cancer. Approximately 10 percent of patients carry BRCA1 or BRCA2 mutations. Both of these are DNA repair genes and are needed by both normal tissue and tumor tissue.

Among patients with germline mutations of BRCA, tumor cells have little BRCA activity. One allele was lost with the germline mutation, and the remaining allele was lost when the cells became cancerous. So the tumor cells are dependent upon this alternate pathway known as PARP, which in normal tissue is relatively inconsequential because of the presence of a much more powerful BRCA DNA repair pathway. PARP inhibitors block this alternate pathway, which tumor cells are now dependent upon in the face of the BRCA mutation.

When PARP is inhibited, suddenly cancer cells have no ability to repair their DNA and undergo apoptosis. A Phase II study has shown dramatic responses with single-agent olaparib, a PARP inhibitor, in advanced chemotherapy-refractory ovarian cancer with BRCA mutation (Audeh 2010; [4.1]).

Theoretically, PARP inhibitors should work well as single agents and in combination with chemotherapy for patients with germline BRCA1 or BRCA2 mutations. Patients with serous ovarian tumors do not have germline mutations of BRCA1 or BRCA2. However, they may have relatively inactive BRCA pathways, which may have been blocked by mechanisms such as methylation. Essentially, these tumors may be functioning as if they do not have active BRCA pathways and thus may be sensitive to PARP inhibitors. So PARP inhibitors will be studied not only for patients with BRCA mutations but also for these patients with sporadic ovarian cancer and BRCAness.

4.1

Efficacy and Safety of Olaparib in Chemotherapy-Refractory Ovarian Cancer with BRCA1/BRCA2 Germline Mutation

RECIST response rate[1]	Clinical benefit rate[1,2]	Grade III/IV nausea[1]	Grade III/IV fatigue[1]
33%	52%	6%	3%

[1] Response rates, benefit rates and toxicities are with olaparib 400 mg PO BID (n = 33);
[2] Clinical benefit rate: RECIST response and/or confirmed ≥50 percent decline in CA125

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

Track 11

DR LOVE: What do we know about anti-HER2 therapy in ovarian cancer and pertuzumab specifically?

DR OZOLS: Pertuzumab is a different type of monoclonal antibody and is a HER dimerization inhibitor. In a Phase I study pertuzumab demonstrated antitumor activity (Agus 2005). Data have also been reported with chemotherapy/pertuzumab (Makhija 2010), and efforts have been made to identify markers that could predict response to pertuzumab (Gordon 2006; Makhija 2010; [4.2]). ■

4.2

Progression-Free Survival with the Addition of Pertuzumab to Gemcitabine (Gem) in Platinum-Resistant Ovarian Cancer, Including Analysis by HER3 mRNA Expression

Progression-free survival	Gem/placebo	Gem/pertuzumab	HR	*p*-value
All pts (n = 65, 65)	2.6 mo	2.9 mo	0.66	0.0708
Primary platinum resistant (n = 42, 48)	1.5 mo	2.9 mo	0.62	0.0405
HER3 < 50th percentile (n = 35, 26)	1.4 mo	5.3 mo	0.32	0.0002
HER3 > 50th percentile (n = 24, 37)	5.5 mo	2.8 mo	1.68	0.0844

Makhija S et al. *J Clin Oncol* 2010;28(7):1215-23.

SELECT PUBLICATIONS

Agus DB et al. **Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer.** *J Clin Oncol* 2005;23(11):2534-43.

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.

Bookman MA et al. **Evaluation of monoclonal humanized anti-HER2 antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of HER2: A phase II trial of the Gynecologic Oncology Group.** *J Clin Oncol* 2003;21(2):283-90.

Burger RA et al. **Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study.** *Proc ASCO* 2010;**Abstract LBA1**.

Gordon MS et al. **Clinical activity of pertuzumab (rhuMAb 2C4), a HER dimerization inhibitor, in advanced ovarian cancer: Potential predictive relationship with tumor HER2 activation status.** *J Clin Oncol* 2006;24(26):4324-32.

Makhija S et al. **Clinical activity of gemcitabine plus pertuzumab in platinum-resistant ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.** *J Clin Oncol* 2010;28(7):1215-23.