INTERVIEW

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Tracks 1-20

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Track 20 Risk of platinum-related allergic reaction with subsequent platinum re-exposure in OC

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: Would you describe the Phase III GOG-0218 trial?

DR MATULONIS: The GOG-0218 trial was initiated a few years ago to evaluate chemotherapy with or without bevacizumab followed by maintenance bevacizumab for patients with ovarian cancer who underwent up-front debulking surgery (1.1). The trial enrolled more than 1,800 patients and involved three arms. This is an important study because it is the first time that a targeted therapy has been added to the backbone of up-front chemotherapy in ovarian cancer.

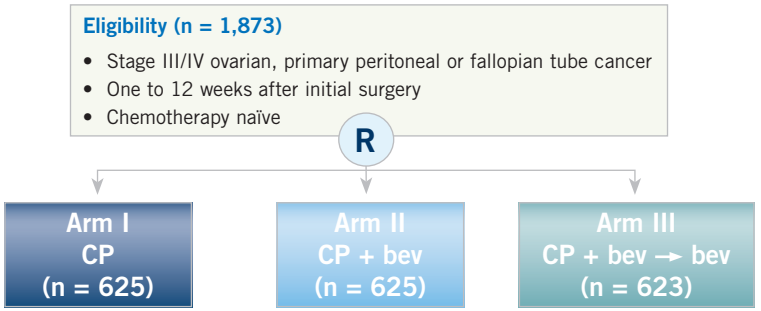
DR LOVE: What did they see in terms of outcomes?

DR MATULONIS: The bottom line is that no difference in progression-free survival (PFS) or overall survival was evident when chemotherapy alone was compared to chemotherapy administered with bevacizumab. However, when you compare chemotherapy alone to chemotherapy with bevacizumab followed by maintenance bevacizumab an improvement in PFS of approximately four months is observed, which was the goal of the study (Burger 2010; [1.2]).

I believe this is a trial in which we must watch the efficacy data over time and let them mature. When paclitaxel was initially added to the platinum agent, the change in PFS was six or eight months, but that translated into a year of overall survival benefit with longer follow-up. Therefore, we must watch this and see if longer follow-up might change the PFS data or if an overall survival difference might emerge.

1.1

GOG-0218: A Phase III Trial of Chemotherapy versus Chemotherapy/ Bevacizumab (Bev) with or without Maintenance Bev



CP = carboplatin AUC 6, paclitaxel 175 mg/m^2; six three-week cycles
CP + bev = CP + bev 15 mg/kg with each cycle of CP
CP + bev → bev = CP + bev followed by 16 three-week cycles of bev 15 mg/kg

Burger RA et al. *Proc ASCO* 2010;**Abstract LBA1**.

1.2

GOG-0218 Study: Primary Endpoint — Progression-Free Survival (PFS)

	Arm I CP (n = 625)	Arm II CP + bev (n = 625)	Arm III CP + bev → bev (n = 623)
Patients with event (%)	67.7	66.9	57.8
Median PFS, months	10.3	11.2	14.1
Hazard ratio	—	0.908	0.717
One-sided *p*-value	—	0.080	<0.0001

CP = carboplatin/paclitaxel; bev = bevacizumab

Burger RA et al. *Proc ASCO* 2010;**Abstract LBA1**.

DR LOVE: Have you integrated these data into the up-front management of ovarian cancer?

DR MATULONIS: Certain patients will have contraindications, such as those with poorly controlled hypertension or those who would not be compliant in monitoring their blood pressure. I would caution patients who have a wound complication or those who underwent a bowel resection.

The trial was developed with a goal of identifying a four-month change in PFS, which is what occurred, so it does meet significance, and I believe a benefit exists. For the patients who are eligible to receive bevacizumab — such as those who have high-grade serous cancer or in whom disease is left behind after surgery — I certainly talk to them about the possibility of administering bevacizumab during chemotherapy and as maintenance therapy.

Tracks 7-8

DR LOVE: What about bevacizumab in recurrent ovarian cancer?

DR MATULONIS: I have no doubt that bevacizumab is effective in recurrent ovarian cancer (Burger 2007; Cannistra 2007). However, the risks — which are different in recurrent disease versus in the up-front setting — must be considered, especially in terms of gastrointestinal (GI) perforations. I tend to administer it to patients who have chemotherapy-resistant disease because another chemotherapy agent would have less utility.

Regarding the extent of disease, an ideal patient should have nodal recurrence, such as a few para-aortic nodes or pelvic lymph nodes, and not have diffuse peritoneal disease.

Bevacizumab can shrink tumors and put a cap on tumor growth. It is an agent that patients can tolerate well for a while. Some of the original data sets provided evidence of a decrease in ascites with bevacizumab. However, our patient population has changed, and currently we do not see many patients

with large-volume ascites, which may be attributable to the increased use of bevacizumab.

Tracks 9-11

DR LOVE: What are your thoughts on PARP inhibitors for the treatment of ovarian cancer?

DR MATULONIS: The data on PARP inhibitors that caught my attention were from the study of olaparib for patients with ovarian cancer with or without BRCA mutations (Gelmon 2010). It is a well-designed trial and provided objective evidence that patients without BRCA mutations could respond to a PARP inhibitor as monotherapy. This opens up the field of PARP inhibitors for a broader population of patients with ovarian cancer.

Another PARP inhibitor, iniparib, is being evaluated in ovarian cancer in ongoing Phase II trials with carboplatin/gemcitabine for platinum-sensitive and platinum-resistant ovarian cancer (1.3).

DR LOVE: Would you discuss the data comparing carboplatin/gemcitabine to carboplatin/paclitaxel in the initial management of ovarian cancer?

DR MATULONIS: The oral presentation at ASCO 2010 compared carboplatin/gemcitabine to carboplatin/paclitaxel as up-front induction treatment for ovarian cancer. For patients who achieved complete responses, they administered maintenance therapy after initial induction treatment.

The bottom line is that no difference was observed between carboplatin/gemcitabine and carboplatin/paclitaxel in the initial management of ovarian cancer (Teneriello 2010; [1.4]).

I believe that carboplatin/paclitaxel remains the standard, but now we have alternatives and therefore flexibility in treatment approach. If a patient either develops a significant reaction to paclitaxel or prefers to avoid alopecia, for example, in those settings carboplatin/gemcitabine could be used up front. ■

1.3 Ongoing Trials of Iniparib (BSI-201) in Advanced Ovarian Cancer

Clinicaltrials.gov identifier	Phase	N	Eligibility	Treatment
NCT01033123	II	41	One prior platinum-containing regimen; platinum sensitive	Carboplatin, gemcitabine, iniparib
NCT01033292	II	48	One prior platinum-containing regimen; platinum resistant	Carboplatin, gemcitabine, iniparib
NCT00677079	II	35	One prior platinum-containing regimen; confirmed BRCA1/2	Iniparib

www.clinicaltrials.gov, January 12, 2011.

1.4

Phase III Study Comparing Carboplatin/Paclitaxel (TC) to Carboplatin/Gemcitabine (GC) as Up-Front Induction Therapy for Ovarian Cancer (N = 831)

	TC	GC	*p*-value
Median progression-free survival	22.2 months	20.0 months	0.199
Overall response (CR + PR)	71.1%	67.6%	0.771
Complete response (CR)	43.9%	41.0%	0.795
Partial response (PR)	27.2%	26.6%	—
Stable disease (SD)	14.0%	15.8%	—
Disease control rate (CR + PR + SD)	85.1%	83.5%	>0.999
Select adverse events			
Grade 3 or 4 anemia	7.6%	27.4%	0.0001
Grade 3 or 4 thrombocytopenia	11.8%	67.7%	0.0001
Platelet transfusion	0%	2.7%	0.0009
Grade 2 or higher neuropathy	14.0%	2.2%	<0.0001
Grade 2 or 3 alopecia	51%	7.3%	<0.0001

Teneriello MG et al. *Proc ASCO* 2010;**Abstract LBA5008**.

SELECT PUBLICATIONS

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.

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**.

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.

Fong PC et al. **Poly(ADP)-ribose polymerase inhibition: Frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval.** *J Clin Oncol* 2010;28(15):2512-9.

Gelmon KA et al. **Can we define tumors that will respond to PARP inhibitors? A phase II correlative study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer.** *Proc ASCO* 2010;**Abstract 3002**.

Han ES et al. **Predictive and prognostic angiogenic markers in a Gynecologic Oncology Group phase II trial of bevacizumab in recurrent and persistent ovarian or peritoneal cancer.** *Gynecol Oncol* 2010;119(3):484-90.

Teneriello MG et al. **Phase III trial of induction gemcitabine (G) or paclitaxel (T) plus carboplatin (C) followed by elective T consolidation in advanced ovarian cancer (OC): Final safety and efficacy report.** *Proc ASCO* 2010;**Abstract LBA5008**.