INTERVIEW

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Tracks 1-19

Track 1 Risk of Ovarian Cancer Algorithm (ROCA) as a feasible screening tool for OC

Track 2 Fertility preservation in patients with BRCA mutations without OC

Track 3 PARP as a therapeutic target in OC

Track 4 GOG-0218: A Phase III trial of chemotherapy versus chemotherapy/bevacizumab with or without maintenance bevacizumab in the primary treatment of advanced OC

Track 5 BIBF 1120: A multitargeted tyrosine kinase inhibitor being investigated in the initial management of OC

Track 6 Tolerability and side effects of BIBF 1120

Track 7 Current approach to the incorporation of bevacizumab into the treatment of OC

Track 8 VEGF and angiogenesis in OC

Track 9 Farletuzumab: A humanized antibody targeting folate receptor alpha in OC

Track 10 **Case discussion:** A 55-year-old woman with Stage IV OC treated with neoadjuvant chemotherapy followed by surgical debulking

Track 11 EORTC-55971: A Phase III study comparing up-front debulking surgery to neoadjuvant chemotherapy for Stage IIIC/IV OC

Track 12 Principles of surgery in OC

Track 13 **Case discussion:** A 67-year-old woman with Stage IIIC OC has a complete response with initial systemic therapy and is followed with serial CA125 assessments

Track 14 Early treatment of relapsed OC based on CA125 level alone versus delayed treatment based on conventional clinical indicators

Track 15 Efficacy of carboplatin/gemcitabine in recurrent, platinum-sensitive OC

Track 16 Treatment algorithm for the management of OC

Track 17 **Case discussion:** A 62-year-old woman with OC experiences disease recurrence 10 months after initial therapy and then enrolls for a clinical trial investigating bevacizumab for platinum-sensitive disease

Track 18 Efficacy and side effects of paclitaxel versus docetaxel in OC

Track 19 Aflibercept as a novel anti-VEGF agent in OC

Select Excerpts from the Interview

Tracks 5-6

DR LOVE: What are your thoughts on the use of tyrosine kinase inhibitors (TKIs) such as BIBF 1120 in ovarian cancer?

DR COLEMAN: BIBF 1120 is an interesting compound. It is a multitargeted TKI that counts VEGF among its multiple targets. BIBF 1120 also has some fibroblast growth factor inhibition, which makes it interesting in the context of potential VEGF-independent growth.

The agent seems to be well tolerated overall (3.1). We didn't see a large number of patients coming off of the trial because of side effects or adverse events. Study of BIBF 1120 as maintenance therapy continues, and the agent is also moving forward into a first-line Phase III study for patients with platinum-sensitive disease.

3.1 **Randomized Placebo-Controlled Phase II Trial Evaluating BIBF 1120 as Maintenance Therapy After Treatment of Relapsed Ovarian Cancer**

	BIBF 1120 (n = 43)	Placebo (n = 40)	Hazard ratio	*p*-value
Efficacy				
Progression-free survival at 36 weeks	14.3%	5.0%	0.68	0.09
Adverse events				
Diarrhea	9%	2%	—	—
Vomiting	5%	2%	—	—
Hypertension	5%	0%	—	—
Elevated LFTs	51%	7%	—	—

Ledermann JA et al. *Proc ASCO* 2009;**Abstract 5501**.

Track 9

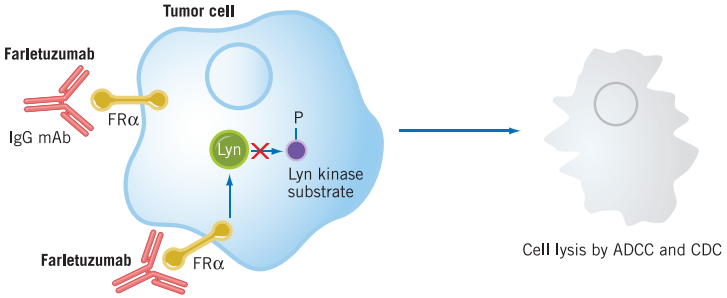
DR LOVE: What are your thoughts on the humanized monoclonal antibody farletuzumab?

DR COLEMAN: Farletuzumab targets the folate receptor alpha, which is overexpressed in more than 90 percent of ovarian cancer cells and is relatively absent in other cells. This makes farletuzumab a selective agent and a candidate for administration alone or in combination with chemotherapy for patients with ovarian cancer. We expect the agent would have low additional toxicity.

The mechanism of action seems to function through complement-dependent and antibody-dependent cytotoxicities (3.2).

3.2

Farletuzumab: Bimodal Mechanism of Action



Farletuzumab, a humanized monoclonal antibody (mAb), demonstrates a high affinity to the folate receptor alpha (FRα). Binding of mAb to FRα results in a bimodal mechanism of action to suppress tumor growth: (1) promotion of cell lysis by antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) and (2) decreased cellular proliferation through the inhibition of Lyn kinase substrate phosphorylation (P).

Adapted from White AJ et al. *Proc ASCO* 2010;**Abstract 5001**.

DR LOVE: How does farletuzumab's effect compare to some of the antifolate chemotherapy agents, and could they be administered together?

DR COLEMAN: You could administer these agents together as they work on different axes. Other antifolate agents act on the enzymes involved with folate metabolism, so they work through a completely different mechanism of action. At ASCO 2010, our group presented Phase II trial data on farletuzumab (White 2010; [3.3]). An interesting take-home message from the presentation was the fact that when patients received farletuzumab in combination with the chemotherapy they received in the first-line setting, 20 to 25 percent fared better when farletuzumab was added to their chemotherapy backbone. So their secondary platinum-free interval was longer than their first. I'm extremely interested in evaluating the data that I hope will emerge from the combinations of farletuzumab with paclitaxel because we do see some impressive synergy with farletuzumab and the taxanes.

3.3

Phase II Trial: Activity of Farletuzumab and Carboplatin/Paclitaxel in Platinum-Sensitive Relapsed Ovarian Cancer (n = 44)

CA125 normalization	RECIST response (CR + PR)	RECIST patient benefit (CR + PR + SD)	Median progression-free interval by CA125 criterion
89%	70%	93%	10 months

CR = complete response; PR = partial response; SD = stable disease

White AJ et al. *Proc ASCO* 2010;**Abstract 5001**.

Track 19

DR LOVE: Would you describe the novel anti-VEGF agent aflibercept, or VEGF Trap, and compare its mechanism of action to that of bevacizumab?

DR COLEMAN: Aflibercept, or VEGF Trap, was designed as a fusion protein to essentially bind the VEGF binding domains of VEGFR1 and VEGFR2 into a fusion decoy receptor. Aflibercept has an IgG base, but it has the second domain of VEGFR1 and the third domain of VEGFR2, which provides an exquisite affinity for VEGF.

Aflibercept has a number of similarities to bevacizumab in that it targets VEGF, but it also has some differences. One of the major differences between the two compounds is that aflibercept binds VEGF one to one, whereas bevacizumab, being a monoclonal antibody, can bind several molecules at the same time.

Whether that will change the toxicity profile — for instance, with regard to clotting — is difficult to predict. A Phase II trial (NCT00436501) we are conducting with aflibercept is approaching completion, and so far, from our experience the toxicity profiles appear similar — hypertension, neurological symptoms and renal symptoms. ■

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