INTERVIEW

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Tracks 1-14

Select Excerpts from the Interview

Track 5

DR LOVE: What is the mechanism of action of the novel agent farletuzumab in ovarian cancer?

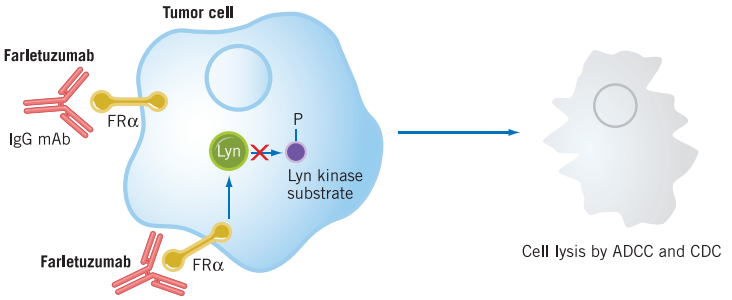
DR ARMSTRONG: Farletuzumab is an interesting targeted agent. Folate is taken up into cells by two mechanisms: one is the folate receptor alpha and

the other is reduced folate carrier. The folate receptor alpha is highly overexpressed in ovarian cancer, on the order of 90-plus percent, but is largely absent from normal tissues.

Farletuzumab is an antibody that targets folate receptor alpha (2.1), and because of the differential expression of folate receptor alpha on ovarian cancer cells and normal tissues, folate can still penetrate normal cells naturally through the reduced folate carrier.

2.1

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**.

2.2

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

The response rate among patients with a first progression-free interval of less than 12 months was unexpectedly high, comparable to that for patients with a first progression-free interval of more than 12 months.

Preliminary data for this study also indicated that farletuzumab with carboplatin/paclitaxel significantly increases the objective response rate compared to the objective response rates in historic data with carboplatin/paclitaxel in platinum-sensitive first-relapse ovarian cancer and increases the duration of second remission compared to first remission.

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

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

A Phase II trial investigating farletuzumab enrolled patients with low-volume or asymptomatic disease to receive single-agent farletuzumab alone, and those with high-volume or symptomatic disease went on to receive chemotherapy combined with farletuzumab. The overall CA125 response and RECIST response to the combination are quite high (White 2010; [2.2]).

In addition, in 21 percent of the patients receiving farletuzumab/chemotherapy, the second progression-free interval was longer than their initial progression-free interval with chemotherapy alone. These data have led to ongoing trials in platinum-resistant disease, in addition to the registrational study in platinum-sensitive disease with paclitaxel and carboplatin.

Track 6

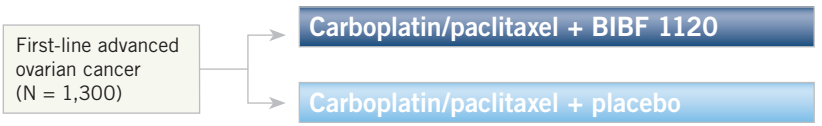
DR LOVE: What are your thoughts on anti-angiogeneic tyrosine kinase inhibitors being evaluated in ovarian cancer?

DR ARMSTRONG: Many oral angiogenesis inhibitors are currently in development for ovarian cancer.

BIBF 1120 is one of these VEGF tyrosine kinase inhibitors, and it is being investigated in combination with chemotherapy in a large, placebo-controlled, randomized Phase III study in the front-line management of ovarian cancer (2.3). Another oral agent currently being investigated in a Phase II setting is sorafenib in combination with bevacizumab.

2.3

Randomized Placebo-Controlled Phase III Trial of BIBF 1120 in Combination with Carboplatin/Paclitaxel as First-Line Treatment for Ovarian Cancer



Primary endpoint is progression-free survival.

www.clinicaltrials.gov. Identifier NCT01015118.

Track 12

DR LOVE: What new research strategies are being used with IP chemotherapy in ovarian cancer?

DR ARMSTRONG: Many clinical trials are investigating carboplatin instead of cisplatin when administering IP chemotherapy. A trial investigating IP carboplatin, IP paclitaxel and IV bevacizumab has been published and demonstrated that the addition of bevacizumab is feasible (Krasner 2010; [2.4]).

In addition, the Gynecologic Oncology Group is investigating the addition of bevacizumab to both IV and IP chemotherapy in a Phase III clinical trial in ovarian cancer (2.5). This trial, GOG-0252, also has a maintenance bevacizumab component that continues until disease progression. ■

2.4

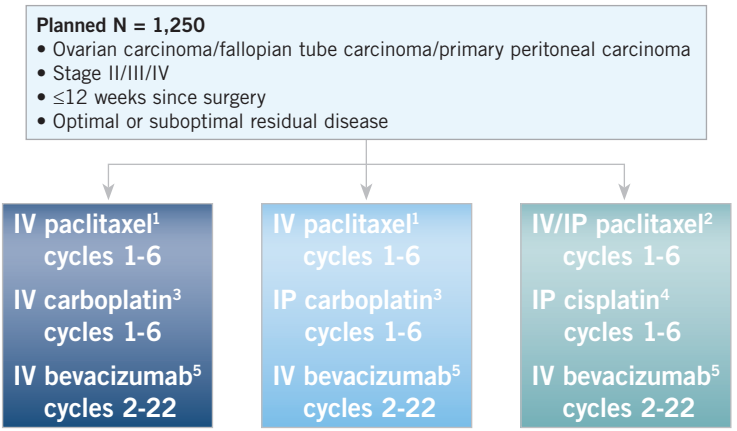
Tolerability of Intraperitoneal Carboplatin and Paclitaxel with Intravenous Bevacizumab (n = 40)

Febrile neutropenia	Grade III-IV neutropenia	Grade III-IV thrombocytopenia	Grade III-IV hypertension	Bowel perforation	Pulmonary emboli
0%	25%	12.5%	0%	0%	5%

Krasner CN et al. *Proc ASCO* 2010;**Abstract 5037**.

2.5

A Phase III Study of Bevacizumab with IV versus IP Chemotherapy in Ovarian, Fallopian Tube and Primary Peritoneal Carcinoma



Primary endpoint is progression-free survival.
Each cycle is 21 days in duration.

[1] Paclitaxel is administered on days 1, 8 and 15; [2] Paclitaxel is administered IV on day 1 and IP on day 8; [3] Carboplatin is administered on day 1 of cycles 1-6; [4] Cisplatin is administered on day 2 of cycles 1-6; [5] Bevacizumab is administered with chemotherapy on day 1 of cycles 2-6 and alone on day 1 of cycles 7-22.

www.clinicaltrials.gov. Identifier NCT00951496.

SELECT PUBLICATIONS

Krasner CN et al. **Tolerability and pharmacokinetics of intraperitoneal carboplatin and paclitaxel with intravenous bevacizumab.** *Proc ASCO* 2010;**Abstract 5037**.

White AJ et al. **Efficacy and safety of farletuzumab, a humanized monoclonal antibody to folate receptor alpha, in platinum-sensitive relapsed ovarian cancer subjects: Final data from a multicenter phase II study.** *Proc ASCO* 2010;**Abstract 5001**.