Prognostic and predictive blood-based biomarkers in patients with advanced epithelial ovarian cancer treated with carboplatin–paclitaxel ± bevacizumab: Results from GOG-0218.

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Background

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy. Recently, several antiangiogenic agents have demonstrated clinical efficacy and in some cases improved overall survival in select ovarian cancer patients.(1,2) However, these antiangiogenic agents have significant side effects, not all patients respond to the treatment, and ultimately resistance to the treatment develops. Rationally directed antiangiogenic therapy in women with EOC can maximize benefit, while minimizing toxicity and cost of unnecessary treatment. In this study, we used baseline plasma samples from women enrolled on GOG-0218 to validate five pre-specified markers of our plasma angiome panel previously identified as predictive for bevacizumab: interleukin 6 (IL6), angiopoietin 2 (Ang-2), osteopontin (OPN), stromal cell-derived factor-1 (SDF-1), and vascular endothelial growth factor-D (VEGF-D).(3, 4) We hypothesize that plasma levels of these biomarkers could serve as prognostic and predictive biomarkers.

- **Primary objective:**
  Determine whether components of the plasma angiome panel (Ang-2, SDF-1, VEGF-D, OPN, and IL6) are predictive of progression-free survival (PFS), in women with advanced ovarian cancer treated with bevacizumab on GOG-0218.
- **Secondary objectives:**
  Determine whether components of the plasma angiome panel (Ang-2, SDF-1, VEGF-D, OPN, and IL6) are predictive of overall survival (OS) in women with advanced ovarian cancer treated with bevacizumab on GOG-0218.
- **Exploratory objectives:**
  Determine whether components of the plasma angiome panel (Ang-2, SDF-1, VEGF-D, OPN, and IL6) are prognostic for PFS and OS in women with advanced ovarian cancer treated with bevacizumab on GOG-0218.

Methods

- Baseline plasma samples from GOG-0218 samples were available from 752 of 1248 patients. (Table 1)
- Plasma samples were analyzed via multiplex ELISA technology (CiraScan system, Aushon BioSystems) for the 5 pre-specified candidate biomarkers (Ang-2, SDF-1, VEGF-D, OPN, and IL6).
- Biomarkers were initially evaluated as continuous variables and median (high vs. low) values. Biomarkers of interest were further explored at different cut-offs (Quartiles 1-4).
- Prognostic variables, treatment effects, and association with biomarkers were analyzed using Cox proportional hazards regression models for PFS and OS. The results were adjusted for age, stage, debulking status, and performance status.
- Statistical significance was determined using Bonferroni correction for multiple testing (after correction, $P<0.01$ denotes significance). Unadjusted P-values are displayed.

		Biomarker Evaluable Population	Overall Population
	N	**752**	**1248**
AGE	Median (range)	60 (26-89)	60 (22-89)
Stage/ Debulking Status	III (macroscopic, ≤ 1cm)	283 (38%)	437 (35%)
	III (> 1cm)	273 (36%)	499 (40%)
	IV	196 (26%)	312 (25%)
GOG Performance Status	0	362 (48%)	612 (49%)
	1/2	390 (52%)	636 (51%)

Table 1. Demographic and clinical characteristics of the biomarker cohort and overall patient population

Results

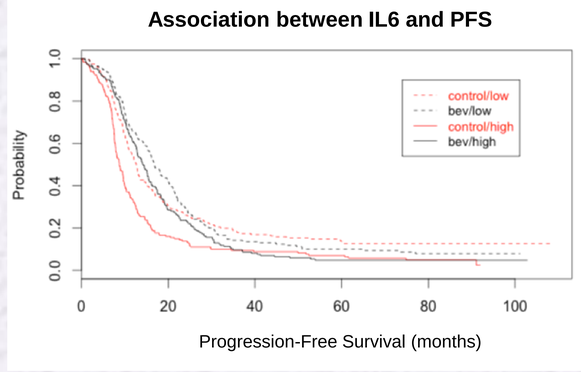
A. Predictive Associations

Marker	PFS *P*-value	OS *P*-value
IL6	0.009	0.005
OPN	0.11	0.14
VEGF-D	0.56	0.70
ANG-2	0.60	0.21
SDF-1	0.50	0.18

B. Prognostic Associations

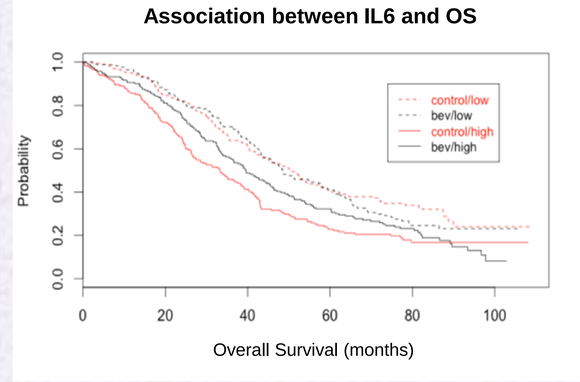
Marker	PFS *P*-value	OS *P*-value
IL6	1.97^{-4}	7.85^{-6}
OPN	4.73^{-7}	3.16^{-9}
VEGF-D	0.71	0.45
ANG-2	0.06	0.01
SDF-1	0.24	0.50

Table 2. Evaluation of Ang-2, SDF-1, VEGF-D, OPN, and IL6 in women enrolled on the GOG-0218 trial. A.) P-value for interaction with bevacizumab treatment (predictive efficacy) was explored based on continuous values; multivariate adjusted for cofounders – age, stage, debulking, and performance status. **B.)** Prognostic associations were evaluated using a threshold of $P=0.01$ to correct for multiple testing**.** IL6 was found to be prognostic for PFS ($P=1.97^{-4}$) and OS ($P=7.85^{-6}$). OPN was prognostic for PFS ($P=4.73^{-7}$) and OS ($P=3.16^{-6}$).



IL6	PFS (months)	
	Control	Bev
≤ median	12.6	16.9
> median	8.7	14.2

Figure 1. Association between IL6 and PFS. EOC patients with high IL6 levels (> median) treated with bevacizumab had longer PFS (14.2 vs. 8.7 months).



IL6	OS (months)	
	Control	Bev
≤ median	50.7	48.5
> median	33.3	39.6

Figure 2 . Association between IL6 and OS. EOC patients with high IL6 levels (> median) treated with bevacizumab had longer OS (39.6 vs. 33.3 months).

Quartile	N	IL6 level (pg/ml)	PFS (months)	PFS (months)	HR (CI)	Interaction *P*-value
						0.019
Q1	188	<10.0	11.5	20.1	0.79 (0.58-1.07)	
Q2	187	10.0-21.9	13.1	15.3	1.09 (0.81-1.49)	
Q3	187	21.9-49.1	9.4	14.1	0.73 (0.54-0.98)	
Q4	188	>49.1	7.9	14.5	0.62 (0.46-0.83)	

Table 3 . Predictive Associations IL6 Quartiles and PFS Outcomes. P-value is for interaction with bevacizumab treatment (predictive efficacy).

Quartile	N	IL6 level (pg/ml)	OS (months)	OS (months)	HR (CI)	Interaction *P*-value
						0.013
Q1	188	<10.0	45.1	59.4	0.83 (0.59-1.19)	
Q2	187	10.0-21.9	58.1	45.8	1.41 (0.99-2.0)	
Q3	187	21.9-49.1	38.7	39.6	0.98 (0.71-1.36)	
Q4	188	>49.1	24.8	39	0.69 (0.50-0.96)	

Table 4. Predictive Associations IL6 Quartiles and OS Outcomes. P-value is for interaction with bevacizumab treatment (predictive efficacy).

Conclusions

❖Our analysis indicates that IL6 and OPN are prognostic for PFS while IL6, OPN, and ANG-2 are prognostic for OS in women with advanced EOC.

❖Data suggest that IL6 is highly predictive of therapeutic benefit from bevacizumab when combined with standard platinum and taxane-based chemotherapy. IL6 was found to be predictive for both PFS and OS.

❖EOC patients with high IL6 levels (> median; 21.9 pg/ml) treated with bevacizumab had longer PFS (14.2 vs. 8.7 months) and OS (39.6 vs. 33.3 months) compared to those treated with chemotherapy alone.

❖Our data demonstrates that IL6 is highly predictive of therapeutic benefit from bevacizumab in women with advanced epithelial ovarian cancer. Our findings are consistent with other IL6 data that have been previously reported from two trial datasets.

❖Previous data regarding IL6 as a potential predictor for anti-angiogenic agent benefit demonstrate that:

- High IL6 levels were predictive for survival benefit in patients with metastatic renal cell carcinoma treated with bevacizumab and interferon alfa.(3)
- Risk scores based on IL6 and hepatocyte growth factor identified patients who benefitted most from the addition of bevacizumab.(3)
- High IL6 levels were predictive for improved PFS benefit from pazopanib compared with placebo in patients with metastatic renal cell carcinoma.(5)

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