We read with interest the proteomic study by Collinson and colleagues (1), proposing a biomarker signature with promising ability in predicting benefit from the addition of bevacizumab to standard chemotherapy in epithelial ovarian cancer (EOC). The identification of predictors of benefit from bevacizumab is one of the most pressing priority in medical oncology, as indications for its use have gradually increased and the number of candidate patients has relevantly grown. We also appreciate that authors point out the importance of exploiting phase III randomized trials to throw light on this until today elusive challenge and claim the validation phase as a crucial step in the development of biomarkers.

One of the “new” indications of bevacizumab concerns its prosecution beyond disease progression in metastatic colorectal cancer, based on results of phase III ML18147 (2) and BEBYP (3) trials, both randomizing patients progressed to first-line chemotherapy plus bevacizumab to prosecute the antiangiogenic or not, in combination with a switched second-line chemotherapy regimen.

On the basis of our previous findings about the modulation of circulating angiogenesis-related markers during chemotherapy plus bevacizumab (4), we took advantage of samples collected from a subgroup of patients enrolled in BEBYP trial to assess the role of VEGFR-2 in predicting benefit from prosecuting bevacizumab beyond progression. In the group of 30 patients with high VEGFR-2 levels (>median value, 6.3 ng/mL) the prosecution of bevacizumab was associated with a significant benefit in progression-free survival [PFS; median, 10.4 vs. 3.4 months; HR, 0.24; 95% confidence interval (CI), 0.10–0.58; \(P = 0.002\)]. Conversely, this benefit was not evident in the group of 29 patients with VEGFR-2 levels below the median value (5.4 vs. 5.0 months; HR, 0.98; 95% CI, 0.45–2.11; \(P = 0.956\); Fig. 1). Results of this exploratory subgroup analysis are strengthened by the significant interaction between VEGFR-2 levels and the effect of bevacizumab (\(P = 0.036\)).

This is the third subgroup analysis of a randomized trial highlighting the potential predictive impact of circulating VEGFR-2 levels, because both AVADO (5) trial in HER-2–negative metastatic breast cancer and BEATRICE (6) trial in adjuvant triple-negative breast cancer actually produced consistent results.

From a biologic perspective, a potential explanation may be recognized in preclinical data, evidencing that VEGFR-2 plasma levels are modulated by VEGF, as a result of ligand-induced downregulation of VEGFR-2 expression on cell surface (7). The inverse relation of plasma VEGF and VEGFR-2 levels would lead to consider circulating VEGFR-2 as a surrogate biomarker of tumor “VEGF-dependency” that is not affected, differently from VEGF, by methodologic issues, such as the presence of different isoforms.

We were wondering whether VEGFR-2 was tested in the exploratory cohort of 10 patients preliminarily analyzed by Collinson and colleagues. Probably, it was actually assessed...
but was not identified among the most promising markers. Nevertheless, the power to identify a statistically significant difference among responders and nonresponders was rather low due to the small sample size of the exploratory cohort and the multiple testing procedure. Therefore, we would anyway encourage the authors to take advantage of their samples to validate the predictive impact of VEGFR-2 levels in the setting of EOC, to further investigate the role of this potentially clinically relevant marker.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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