Impact of Prior Bevacizumab Treatment on VEGF-A and PlGF Levels and Outcome Following Second-Line Afibercept Treatment: Biomarker Post Hoc Analysis of the VELOUR Trial

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ABSTRACT

Purpose: Afibercept is a targeted anti-VEGF therapy used to treat patients with metastatic colorectal cancer (mCRC) following progression on oxaliplatin-based regimens. This post hoc study evaluated the effect of prior bevacizumab treatment and growth factor levels on patient outcomes associated with afibercept in the VELOUR phase III trial.

Experimental Design: Baseline biomarker plasma concentrations were measured using a bead-based multiplex assay. Patients were grouped according to prior bevacizumab treatment, second-line treatment, and serum biomarker concentrations, and analyzed for overall survival (OS) and progression-free survival (PFS).

Results: Plasma samples were available for 553 patients (placebo n = 265; afibercept n = 288), of which 169 had received prior bevacizumab. Nine biomarkers implicated in angiogenesis or bevacizumab resistance correlated with prior bevacizumab therapy.

Introduction

Colorectal cancer is the second most frequently diagnosed cancer and the second leading cause of cancer-related deaths worldwide (1). While patients diagnosed with localized colorectal cancer have a 5-year survival rate of approximately 90%, those diagnosed with distant metastases have far poorer outcomes with a 5-year survival rate of just 13.3% reported in the United States (2, 3). Overall survival (OS) for patients with metastatic colorectal cancer (mCRC) has markedly improved over the last 2 decades, with median OS often surpassing 30 months, largely due to the addition of targeted therapies (4, 5). However, patients with mCRC often become unresponsive to treatment for patients with bevacizumab-induced resistance.

VEGF-A and placental growth factor (PlGF) were the most significantly increased in patients who had received prior bevacizumab compared with those who had not received prior bevacizumab. In the placebo group, patients with high VEGF-A (>144 pg/mL) levels at baseline had worse OS and PFS compared with patients with lower levels at baseline (9.6 vs. 12.9 months). This was also seen in patients who received placebo and had high baseline PlGF (>8 pg/mL; 9.7 vs. 11.7 months). In the afibercept group, prolonged OS and PFS were observed regardless of baseline VEGF-A or PlGF levels.

Conclusions: High VEGF-A and PlGF serum levels may underlie development of resistance to bevacizumab in patients with mCRC. Afibercept retains its activity regardless of baseline VEGF-A and PlGF levels and may be an effective second-line treatment for patients with bevacizumab-induced resistance.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

There is a current unmet need in the field of metastatic colorectal cancer to identify which patients will benefit from the different treatment regimens available. This post hoc study analyzed biomarker data retrieved from patients on the phase III VELOUR trial. Patients had improved survival outcomes associated with afibbercept compared with placebo, regardless of prior bevacizumab treatment, which suggests that challenging patients with an alternative VEGF inhibitor is a viable treatment option. Furthermore, VEGF-A and placental growth factor (PIGF) were identified as potential biomarkers of bevacizumab resistance. However, patients responded to afibbercept regardless of baseline VEGF-A and PIGF levels. This supports the hypothesis that afibbercept is beneficial for patients who have received prior bevacizumab because of its broader anti-VEGF inhibition.

Advances in molecular biology and the understanding of colorectal carcinogenesis have provided opportunities to identify biomarkers that contribute to improved diagnostic, prognostic, and predictive treatment response information, which may have the potential to improve patient outcomes (22–25). Although several biomarkers have been identified to help guide treatment decisions for colorectal cancer (8, 13, 26), clinically relevant biomarkers are still scarce, with the majority of therapeutic considerations made regardless of individual characteristics (27). RAS and BRAF mutation status, primary tumor location, and microsatellite instability (MSI) have been validated as biomarkers and are used clinically to recommend treatment strategies for patients with mCRC (8, 13, 28). For example, patients with MSI are candidates for immune checkpoint inhibitors and patients with left-sided, KRAS and NRAS wild-type tumors derive greater benefit with anti-EGFR therapy (8, 13). Currently, no biomarkers have been validated to determine which patients with mCRC would benefit the most from anti-VEGF therapies. Post hoc data from the VELOUR study suggest that afibbercept may prolong survival in patients with BRAF mutations (29). Recent studies of patients treated with antiangiogenic therapies suggest that angiogenic plasma markers may have some prognostic or predictive value (30, 31).

The objective of this post hoc analysis was to investigate the effect of plasma growth factor levels on patient outcomes in patients with mCRC treated with afibbercept versus placebo in the VELOUR trial, according to prior bevacizumab treatment.

Materials and Methods

VELOUR study

Details of the VELOUR trial, including patient eligibility, trial design, randomization, dose administration, and statistical analyses have been published previously (21). Briefly, VELOUR was a phase III, randomized, placebo-controlled study investigating the efficacy of afibbercept plus FOLFIRI in patients with mCRC who had disease progression while receiving, or after completing, an oxaliplatin-based regimen. Patients were randomized to receive either afibbercept 4 mg/kg (n = 612) or placebo (n = 614) intravenously (i.v.), over 1 hour on day 1 every 2 weeks, followed immediately by the FOLFIRI regimen (irinotecan 180 mg/m² i.v. over 90 minutes, with leucovorin 400 mg/m² i.v. over 2 hours, followed by 5-fluourouracil (FU) 400 mg/m² bolus and FU 2,400 mg/m² continuous infusion over 46 hours), until disease progression or unacceptable toxicity. Randomization was stratified according to prior therapy with bevacizumab (yes or no) and Eastern Cooperative Oncology Group performance status (ECOG PS; 0, 1, or 2; ref. 21).

This study was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from each subject or each subject’s guardian. The human investigations were performed after approval by an institutional review board and in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Biomarker measurement

Blood samples (4 mL) were collected in citrate phosphate dextrose tubes and were centrifuged at 4°C at 2,000 g for 20 minutes. Plasma was transferred into two polypropylene screw cap tubes and frozen immediately at −80°C, within 1 hour after the puncture. All specimens were stored frozen until shipped to central laboratory for analysis. Plasma concentrations of 98 angiogenic factors and inflammatory cytokines were measured centrally prior to treatment using Luminex Technology (98 plasma proteins) and ELISA for VEGF, FGF-acidic, and PIGF. The Myriad Multiplex Assay Rules Based Medicine approach used for the 98 analyses is based on the capture–sandwich format using capture antibodies attached to fluorescently encoded microspheres. After capture of antigen from a biological sample, the antigen was then detected using specific detection antibodies coupled to a fluorescent probe.

Biomarkers with >70% of values below the lower limit of quantification were excluded from the analysis. This allowed to keep a majority of biomarkers in the analysis, removing only those with very high percentage of values below the lower limit of quantification. The intention-to-treat (ITT) population included all patients who gave informed consent and were randomized to a treatment arm, while the biomarker population included all treated patients from the ITT population who had a plasma sample drawn and successfully analyzed at baseline (32).

Statistical analysis

Correlation analysis between biomarkers and clinical variables was performed using Pearson correlation for association between numeric variables and using ANOVA for association between numeric and categorical variables. P values were adjusted using Benjamini–Hochberg procedure to control FDR with a cutoff equal to 0.05. Patients were stratified into four groups according to prior bevacizumab treatment status (yes vs. no) and second-line treatment (afibbercept vs. placebo). Mean levels of growth factors at baseline, median OS, and median PFS were calculated for each of these groups. Median VEGFA and PIGF levels for all patients were 144 pg/mL and 8 pg/mL, respectively. Median OS and PFS were calculated for patients with VEGFA and PIGF levels above the median. HR values for PFS and OS were calculated using a stratified Cox procedure, with ECOG PS and prior bevacizumab as stratification factors. The Breslow method was used to approximate likelihood in presence of ties in the failure time. Analyses were performed using SAS version 9.2 and R version 3.2.3.

Efficacy analysis

On the basis of the previous VELOUR article, OS was defined as the time interval from randomization to death from any cause. PFS was
defined as the interval from randomization to the first observation of disease progression (according to an independent review committee review) or death from any cause (21).

Results

Study population
Of the 1,226 patients in the VELOUR ITT population, 553 had eligible biomarker data at baseline. Of these, 288 and 265 received aflibercept and placebo, respectively (Fig. 1). Baseline characteristics were comparable with those of the ITT population (Supplementary Table S1). Similarly, efficacy outcomes were aligned between the biomarker and ITT populations, with aflibercept prolonging both OS and PFS compared with placebo in the biomarker population (Table 1).

Effect of prior bevacizumab on OS and PFS in the biomarker population
Of the 553 patients analyzed, 169 were previously treated with bevacizumab (aflibercept: n = 90; placebo: n = 79). In the group of patients with no prior bevacizumab, patients who received aflibercept plus FOLFIRI had a median OS of 12.9 months and those who received placebo plus FOLFIRI had a median OS of 11.4 months [HR (95% confidence interval (CI)); 0.80 (0.63–1.01); P = 0.06]. In the group of patients who had received prior bevacizumab, those treated with aflibercept plus FOLFIRI had a median OS of 12.1 months, while those treated with placebo plus FOLFIRI had a median OS of 10.6 months [HR (95% CI), 0.84 (0.59–1.19); P = 0.33].

Similar trends were seen for PFS (Table 1). In the no prior bevacizumab group, patients receiving aflibercept plus FOLFIRI had a median PFS of 6.8 months and patients receiving placebo plus FOLFIRI had a median PFS of 4.9 months, with a HR of 0.79 (0.63–1.00; P = 0.053). In the group of patients who had received prior bevacizumab, patients treated with aflibercept plus FOLFIRI had a median PFS of 7.2 months, while those treated with placebo plus FOLFIRI had a median PFS of 3.9 months, with a HR of 0.71 (0.49–1.04; P = 0.078).

Serum biomarker levels
Of the 98 angiogenic factors analyzed in the biomarker population, nine biomarkers (VEGF-A, PlGF, endoglin, T-cadherin, VEGRF-3, serum amyloid P-component, vitamin D-binding protein, neuropilin-1, and C-reactive protein) implicated in angiogenesis or bevacizumab resistance correlated with prior bevacizumab therapy (P < 0.01; Fig. 2; Supplementary Table S2). This association was most significant for VEGF-A (P = 1e-58) and PlGF (P = 2.8e-13) levels, which were elevated at baseline in patients that had received prior bevacizumab treatment. Mean VEGF-A was 156.9 pg/mL in patients who had not previously received bevacizumab and 758.2 pg/mL in those who had. Mean PlGF was 11.7 pg/mL in patients who had not previously received bevacizumab and 22.0 pg/mL in those who had. Several biomarkers were elevated post-aflibercept treatment, including VEGF-A and PlGF (Supplementary Fig. S1; Supplementary Table S3).

Influence of serum VEGF-A and PlGF on efficacy outcomes
As the factors most significantly associated with prior bevacizumab, patients were grouped on the basis of their baseline serum levels being above or below the median level for VEGF-A (144 pg/mL) and PlGF (8 pg/mL). Among patients treated with placebo, those with baseline VEGF-A plasma levels above the median (>144 pg/mL) had worse OS (9.6 vs. 12.9 months) and PFS (4.0 vs. 5.5 months) compared with
patients who had baseline VEGF-A below the median (Fig. 3A). Similarly, among patients treated with placebo, those with high baseline PlGF (>8 pg/mL) had worse OS (9.7 vs. 11.7 months) and PFS (4.0 vs. 5.3 months) compared with patients who had low baseline PIGF (Fig. 4). However, among the patients treated with aflibercept, OS was similar for patients with high or low baseline VEGF-A (12.5 vs. 12.8 months) or PIGF levels (12.2 vs. 12.8 months). Similarly, PFS was similar for patients who received aflibercept with high or low baseline Table 1. OS, PFS, and growth factor plasma levels in patients from the VELOUR study: comparison of the different patient populations.

<table>
<thead>
<tr>
<th></th>
<th>VELOUR ITT population</th>
<th>VELOUR biomarker population with prior bevacizumab</th>
<th>VELOUR biomarker population with no prior bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 612)</td>
<td>Placebo (n = 288)</td>
<td>Placebo (n = 79)</td>
<td>Placebo (n = 186)</td>
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<tr>
<td>Placebo (n = 614)</td>
<td>Aflibercept (n = 255)</td>
<td>Aflibercept (n = 90)</td>
<td>Aflibercept (n = 198)</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>12.06 (11.07–13.11)</td>
<td>13.50 (12.52–14.95)</td>
<td>11.30 (10.00–12.40)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.817 (0.713–0.937)</td>
<td>0.81 (0.66–0.99)</td>
<td>0.84 (0.59–1.19)</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>4.67 (4.21–5.36)</td>
<td>6.90 (6.51–7.20)</td>
<td>4.30 (3.30–5.80)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.758 (0.661–0.869)</td>
<td>0.77 (0.52–1.14)</td>
<td>0.71 (0.49–1.04)</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td>0.01</td>
<td>0.078</td>
</tr>
<tr>
<td>Mean VEGF-A, pg/mL</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Mean PIGF, pg/mL</td>
<td>NA</td>
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*Adjusted for stratification factors (ECOG and bevacizumab).
VEGF-A (6.9 vs. 6.8 months) or PlGF levels (6.6 vs. 6.9 months). Patients with high baseline VEGF-A had improved OS [HR (95% CI), 0.673 (0.508–0.892); P = 0.00566] and PFS [HR (95% CI), 0.660 (0.493–0.885); P = 0.00521] associated with a fiblercept versus placebo. Similarly, patients with high PlGF had improved OS [HR (95% CI), 0.586 (0.405–0.849); P = 0.00429] and PFS OS [HR (95% CI), 0.535 (0.366–0.783); P = 0.0011]. Patients with low baseline VEGF-A had similar OS [HR (95% CI), 0.974 (0.735–1.291); P = 0.854] and PFS [HR (95% CI), 0.898 (0.681–1.185); P = 0.448] for a fiblercept and placebo. Likewise, patients with low PlGF had similar OS [HR (95% CI), 0.947 (0.746–1.202); P = 0.653] and PFS [HR (95% CI), 0.586 (0.682–1.101); P = 0.24] for a fiblercept and placebo.

This trend was seen in those who had, and had not, received prior bevacizumab (Fig. 5; Supplementary Fig. S2). In the group of patients with no prior bevacizumab and baseline VEGF-A levels > median (144 pg/mL), afibercept was associated with a longer median OS [13.0 vs. 9.4 months; HR (95% CI), 0.56 (0.38–0.82); P = 0.003] and PFS [6.6 vs 4.0 months; HR (95% CI), 0.63 (0.44–0.97); P = 0.032] versus placebo. Patients with baseline VEGF-A > median (144 pg/mL) who had received prior bevacizumab had numerical improvements in OS and PFS associated with afibercept versus placebo [OS: 11.9 vs. 9.8 months; HR (95% CI), 0.83 (0.55–1.24); P = 0.36 and PFS: 7.3 vs. 3.9 months; HR (95% CI), 0.67 (0.43–1.04); P = 0.073].

Similarly, patients with baseline PlGF plasma levels above the median (>8 pg/mL) had higher OS and PFS with afibercept versus placebo, regardless of prior bevacizumab treatment (Fig. 5; Supplementary Fig. S2). In the group of patients with no prior bevacizumab and high PlGF levels, afibercept was associated with significantly improved OS [14.4 vs. 8.65 months; HR (95% CI), 0.42 (0.25–0.72); P = 0.001] and PFS [5.7 vs. 4.2 months; HR (95% CI), 0.53 (0.31–0.89); P = 0.014]. In the group of patients with high PlGF levels who had received prior bevacizumab, afibercept was associated with a significant improvement in PFS [7.3 vs. 3.9 months; HR (95% CI), 0.55 (0.31–0.95); P = 0.031]; however, the OS benefit did not reach significance [OS: 11.5 vs. 10.2 months; HR (95% CI), 0.80 (0.48–1.32); P = 0.38].

Discussion

In the ITT population of the phase III VELOUR trial, afibercept in combination with FOLFIRI was associated with a statistically significant survival benefit over FOLFIRI combined with placebo in patients with mCRC previously treated with oxaliplatin. Although samples could only be analyzed from 553 (45%) patients randomized in VELOUR, baseline characteristics and efficacy outcomes for the biomarker population were consistent with the VELOUR ITT population, suggesting that the biomarker population is representative of the entire VELOUR population (21).

Correlation between key biomarkers implicated in angiogenesis and prior bevacizumab therapy suggests that prior treatment with first-line bevacizumab induced cytokine changes. Of the biomarkers investigated, VEGF-A and PlGF were the most significantly elevated biomarkers at baseline, suggesting that these plasma growth factors correlate with the acquisition of resistance to bevacizumab in patients with mCRC (32). The results presented here support earlier articles reporting that bevacizumab treatment in mCRC, as well as
other cancers, was associated with elevated levels of VEGF-A and PlGF (33–39). In one study, plasma from 32 patients with mCRC had significantly higher VEGF-A and PlGF levels associated with bevacizumab treatment compared with plasma taken from patients before bevacizumab treatment and not receiving bevacizumab (33). Another study evaluated 45 patients with mCRC treated with bevacizumab and 15 who had not received bevacizumab and found that VEGF-A levels increased following bevacizumab treatment. It also identified that much of the VEGF-A was bound to bevacizumab, suggesting that this elevated VEGF-A was inactive. However, the unbound VEGF-A may still provide an escape mechanism and contribute to bevacizumab resistance (34). In a phase II study evaluating 43 patients with mCRC who received first-line bevacizumab plus FOLFIRI, several cytokines and growth factors associated with angiogenesis and myeloid recruitment, including PlGF, were increased compared with baseline. Importantly, these changes occurred before radiographic progression, which could suggest a prognostic role (39). In another study evaluating 25 patients with mCRC treated with FOLFIRI plus bevacizumab, PlGF levels increased. This was also seen in another phase II study evaluating 57 patients with mCRC treated with first-line FOLFOXIRI plus bevacizumab (40). However, in both of these studies, serum concentration of VEGF-A initially decreased after the onset of treatment, which contrasts with previous reports. This may emphasize the deeper role of PlGF, rather than VEGF-A, in bevacizumab resistance (40, 41).

The results of this biomarker post hoc analysis suggest that patients who received placebo and had either high VEGF-A (>144 pg/mL) or PlGF (>8 pg/mL) levels at baseline were associated with worse OS and PFS compared with patients with lower levels at baseline. Conversely, patients treated with aflibercept plus FOLFIRI had prolonged OS and PFS compared with placebo, regardless of VEGF-A and PlGF levels at baseline. The benefit of aflibercept versus placebo was particularly marked in patients with high VEGF-A or PlGF levels at baseline and no prior bevacizumab. This suggests that bevacizumab treatment may lead to increased VEGF-A and PlGF levels, which may contribute to bevacizumab resistance. Importantly, VEGF-A and PlGF levels seem not to be predictive of response to aflibercept, possibly as a result of the latter’s affinity for multiple ligands (18, 19).

The fact that high baseline VEGF-A and PlGF levels in patients treated with placebo are associated with poor outcomes is supported by previous reports (42–44). High VEGF-A serum levels (>5.1 pg/mL) at baseline were associated with worse OS and PFS compared with patients with lower levels at baseline. Conversely, patients treated with aflibercept plus FOLFIRI had prolonged OS and PFS compared with placebo, regardless of VEGF-A and PlGF levels at baseline. The benefit of aflibercept versus placebo was particularly marked in patients with high VEGF-A or PlGF levels at baseline and no prior bevacizumab. This suggests that bevacizumab treatment may lead to increased VEGF-A and PlGF levels, which may contribute to bevacizumab resistance. Importantly, VEGF-A and PlGF levels seem not to be predictive of response to aflibercept, possibly as a result of the latter’s affinity for multiple ligands (18, 19).

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Figure 4.
Efficacy of aflibercept according to PlGF levels. OS (A) and PFS (B) for patients with baseline PlGF above or below the median (8 pg/mL). * adjusted for stratification factors (ECOG, prior bevacizumab).
screening (47). Future studies are needed to confirm the importance of VEGF-A and PlGF serum levels at various stages of the disease and the place of afiblercept in this setting.

Other reports suggest that changes in angiogenic factors during treatment may also be prognostic for response to antiangiogenic therapies. In 23 patients with mCRC who received first-line bevacizumab, early rises in VEGF-A were associated with worse response to therapy (41). In another study, which evaluated the mRNA of several potential biomarkers in circulating tumor cells from patients with mCRC receiving FOLFOX or FOLFIRI plus bevacizumab, improvements in OS and PFS were associated with patients who experienced a decrease of ≥30% in VEGF-A levels or eNOS levels from baseline after 8 weeks (43). Patients with mCRC who received regorafenib also had improved OS and PFS if their VEGF-A levels decreased between baseline and day 21 posttreatment initiation (42). As discussed earlier, afiblercept is associated with an increase in VEGF-A and PlGF, as well as other factors. However, high levels at baseline do not influence response to afiblercept. It may be valuable to evaluate how changes in VEGF-A and PlGF levels following afiblercept affect survival outcomes.

In this study, patients who received afiblercept had similar OS and PFS regardless of baseline VEGF-A or PlGF levels. Afiblercept uniquely targets both VEGF-A and PlGF with a higher affinity than other antiangiogenic therapies, and VEGF-A and PlGF bind afiblercept with higher affinity than their native receptors (48). These findings suggest that tumors progressing under blockade of a single antiangiogenic therapy, such as bevacizumab, most likely use numerous non-VEGF-A mechanisms to sustain their growth. Switching to a different therapy, such as afiblercept, to target these alternative mechanisms may be beneficial.

There are some limitations of this study that must be considered. Biomarkers were collected in only 45% of patients randomized in VELOUR. Although clinical outcomes in the biomarker population were consistent with the VELOUR ITT population, results may not be generalizable to all patients with mCRC.
be extrapolated to the whole VELOUR population. Furthermore, the size of the biomarker population reduced the statistical power of the analysis, possibly explaining the lack of significant differences seen between subgroups. Further populations or studies designed for biomarker analysis are warranted. The analysis focused on VEGF-A and PlGF as these had the strongest association with prior bevacizumab therapy. However, nine other factors were also associated with bevacizumab and should be explored further. The biomarker analysis was also limited to assessing 98 angiogenic factors. It may be that other proangiogenic factors or tumor microenvironment proteins may have contributed to bevacizumab resistance. It was recently reported that tumor-infiltrating neutrophils may confer resistance to bevacizumab (49). Therefore, it may be valuable to expand the type of biomarkers measured. It should also be acknowledged that the patient population used for this analysis received treatment between 2007 and 2011, and therefore the treatment landscape and categorization of colorectal cancer has changed. Consequently, it would be beneficial to validate the findings in a more recent trial population or using patients treated in routine clinical practice. This would also facilitate a more direct comparison between the effect of VEGF-A and PI GF levels and response to different antiangiogenic therapies. The biomarkers under evaluation in this study were only analyzed once pretreatment and during cycles 3, 5, and 30 days following end of treatment. It may be valuable for future studies to evaluate which patients experience changes in VEGF-A and PI GF. Furthermore, it may be beneficial to collect more timepoints so that the changes during pretreatment are also considered.

In summary, this study identifies VEGF-A and PI GF as potential negative prognostic markers in patients with mCRC. As aflibercept targets VEGF-A and PI GF with greater affinity than other antiangiogenic therapies, it may provide benefit to patients who have high VEGF-A or PI GF serum levels. Measurement of VEGF-A and PI GF serum levels is not standard practice; further studies are needed to clarify the importance of these biomarkers in guiding management of patients with colorectal cancer.

References

Disclosure of Potential Conflicts of Interest
E. Van Cutsem is a paid consultant for Array, AstraZeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daichii, Håkonmy, GlassSmithKline, Pierre-Fabre, Incyte, Ipsen, Lilly, MSD, Merck KGA, Novartis, Roche, Servier, Sirtex, and Taibo. C. Paccard is an employee of Sanofi. M. Chiron is an employee of Sanofi. J. Tabernero is a paid consultant for Array Bupharma, AstraZeneca, Bayer, Biocartis, Boehringer Ingelheim, Chugai, Genentech, Inc., Genmab A/S, Halomyne, Imugene Limited, Inflection Biosciences Limited, Ipsen, Kura Oncology, Lilly, MSD, Menarini, Merck Serono, Merrimack, Merus, Molecular Partners, Novartis, Peptogeny, Pfizer, Pharmacia, Pierre Fabre, Proteolysis SL, Rafad Pharmaceuticals, F. Hoffmann-La Roche Ltd, Sanofi, SeaGen, Seattle Genetics, Servier, Symphogen, Taiho, VCN Biosciences, Biocartis, Foundation Medicine, HalioX SAS, and Roche Diagnostics.

Disclaimer
The authors were responsible for all content and editorial decisions and received no honoraria related to the development of this article.

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Bevacizumab, VEGF-A, and PI GF Impact on Afiblercept Response


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