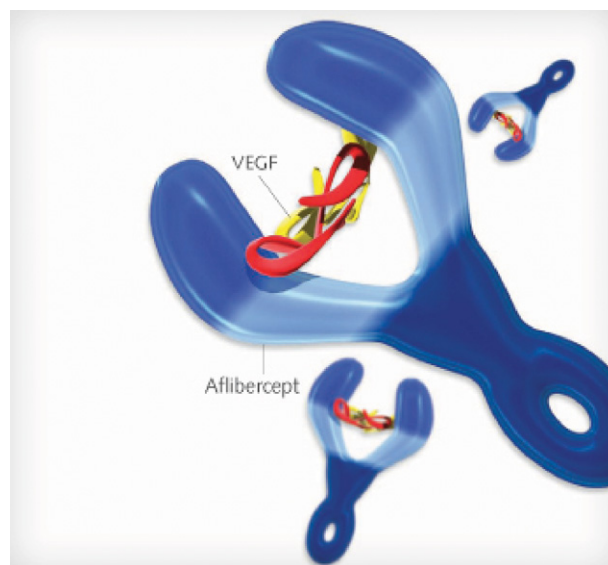


# Aflibercept plus FOLFIRI improves survival in second-line treatment of metastatic colorectal cancer

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**A**flibercept is a recombinant human fusion protein that acts as a decoy receptor to prevent vascular endothelial growth factor (VEGF)-A, VEGF-B, and placental growth factor (PlGF) from interacting with their native receptors, thereby inhibiting angiogenesis (Figure 1). Currently, the humanized monoclonal antibody bevacizumab, which binds to VEGF-A, is the only agent targeting the VEGF pathway that is approved for use in colorectal cancer (CRC). It is used in combination with FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (5-fluorouracil, leucovorin, and irinotecan).

Findings from the recent multinational phase III EFC10262-VELOUR trial have shown that aflibercept is effective in prolonging survival when it is used in combination with FOLFIRI in the second-line treatment of metastatic CRC (mCRC).<sup>1</sup> In the trial, 1,226 patients with mCRC who had previously been treated with an oxaliplatin-containing regimen received FOLFIRI and were randomized to aflibercept 4 mg/kg IV (614 patients) or placebo (612) every 2 weeks. The patients had a median age of 61 years, 59% were male, 98% had ECOG



**FIGURE 1** Aflibercept has a unique structure that facilitates tighter, faster binding to VEGF-A than native VEGF-A receptors. In addition to blocking VEGF-A, aflibercept binds VEGF-B and PlGF, other growth factors implicated in angiogenesis. PlGF has been found to be upregulated in the presence of VEGF-A blockade. Figure from Sanofi Oncology: <http://www.sanofioncology.com/pipeline/aflibercept.aspx>.

## What's new, what's important

Angiogenesis inhibitors have shown significant efficacy in patients with metastatic colorectal cancer, including the anti-VEGF monoclonal antibody bevacizumab and the novel recombinant fusion protein aflibercept. Aflibercept is a chimeric decoy receptor consisting of portions of VEGF receptor 1 (VEGFR1) and VEGFR2 fused with the Fc (fragment crystallizable) region of human IgG1 (immunoglobulin subclass 1). This novel antiangiogenic therapy binds VEGF-A, VEGF-B, and placental growth factor (PlGF) with higher affinity than their native receptors. Aflibercept significantly improved overall survival and progression-free survival compared with placebo and it nearly doubled the overall response

rate compared to placebo. The mechanistic difference between aflibercept and bevacizumab are that bevacizumab binds only to VEGF-A, whereas aflibercept binds to VEGF A, VEGF-B, and PlGF. The binding affinity of aflibercept is almost 800 times greater than that of bevacizumab. Clinical trials have shown that aflibercept is effective even in patients who received bevacizumab previously. The side effects from aflibercept are similar to those of bevacizumab. Hypertension and proteinuria were common. But more serious side effects such as wound dehiscence, gastrointestinal perforation, and pulmonary embolism were not significantly increased.

— Jame Abraham, MD

performance status of grade 0 or 1, 56% had more than 1 metastatic organ, and 30% had received previous bevacizumab therapy.

After a median follow-up of 22.3 months, median overall survival, which was the primary end point of the trial, was 13.5 months in the aflibercept arm, compared with 12.1 months in the placebo arm, representing a significant 18% reduction in risk for death with aflibercept treatment (hazard ratio [HR], 0.82;  $P = .0032$ ). Median progression-free survival was significantly increased to 6.9 months with aflibercept, compared with 4.7 months with placebo (HR, 0.76;  $P = .00007$ ), and aflibercept was associated with a significantly greater overall response rate compared with placebo (19.8% vs 11.1%, respectively;  $P = .0001$ ).

Grade 3 or 4 adverse events with an incidence that was more than 2% greater in the aflibercept arm compared with placebo, were diarrhea, asthenia or fatigue, stomatitis or ulceration, infection, hypertension, gastrointestinal

or abdominal pain, neutropenia or neutropenic complications, and proteinuria. Those side effects with an incidence that was more than 5% greater in aflibercept patients compared with placebo, were diarrhea, neutropenia, asthenia, stomatitis, infection, hypertension, and proteinuria.<sup>2</sup> Discontinuation due to adverse events was markedly more frequent in the aflibercept arm, occurring in 26.6% of aflibercept patients, compared with 12.1% of placebo patients. The most common adverse events resulting in discontinuation among aflibercept patients were asthenia or fatigue, infection, diarrhea, hypertension, and venous thromboembolic events.

#### References

1. Van Cutsem E, Tabernero J, Lakomy R, et al. Intravenous aflibercept versus placebo in combination with irinotecan/5-FU (FOLFIRI) for second-line treatment of metastatic colorectal cancer (MCRC): results of a multinational Phase III trial (EFC10262-VELOUR) (ESMO abstract O-0024). *Ann Oncol*. 2011;22(suppl).
2. Wang T-F, Lockhart AC. Aflibercept in the treatment of metastatic colorectal cancer. *Clin Med Insights Oncol*. 2012;6:19-30.